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Allergic Dermatoses Due to Physical Agents

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PREFACE

FREQUENT WITNESSES though they may be of unusual biologic phenomena, most physicians are intrigued again and again by some of the clinical manifestations that characterize cutaneous allergic hypersensitivities to physical agents.

A pertinent example of these striking phenomena is urticarial hypersensitivity to light, where after only a few seconds' exposure to sunlight the skin presents immediately a pronounced erythema, confined sharply to the area of exposure and followed shortly by the development of a wheal and a very pronounced flare. Writing produced by slight pressure of the fingernail or a tongue blade on the skin of patients with urticarial dermographism is another example. However, in addition to being fascinating from the morphologic viewpoint, hypersensitivities to physical agents also have the greatest theoretic *interest* and are particularly suitable for certain types of studies dealing with allergic sensitization of the skin. This *is due to* the fact that reactions produced by skin test exposures to cold, heat, light and trauma duplicate frequently the actual clinically occurring lesions, in contrast with skin tests in allergic hypersensitivities to *chemical* agents, which usually have to be performed under highly artificial conditions and often involve traumatic techniques that obscure the allergic response itself, as, for instance, in the intracutaneous test.

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CONTENTS

As will be seen from the papers in this symposium, a sharp delineation between allergic and nonallergic hypersensitivities to physical agents is not always possible. An allergic basis may be established clearly for some of these hypersensitivities, while in others proof of a *specific immunologic mechanism* may be weak or entirely lacking. The present text does not claim to resolve the many existing doubts in this field, nor does it cover the existing knowledge in a complete and an exhaustive manner. Rather, it is hoped that it will serve as an outline of what is known and, equally important, of the tremendous gaps in our knowledge of this exceptionally interesting but relatively unexplored segment of immunology.

RUDOLF L. BAER, M.D.

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1

The Present Status of Differentiation of Allergic and Nonallergic Hypersensitivity to Physical Agents

RUDOLF L. BAER, M.D.
New York City

THE ALLERGIC ETIOLOGY of many dermatoses can be established with little or no difficulty. For example, in allergic eczematous contact dermatitis, allergic urticaria, some allergic drug eruptions and in many cutaneous allergic changes due to infectious micro-organisms, the role played by the allergic mechanism is no longer the subject of serious doubt. However, in certain other dermatoses, even though an allergic mechanism appears to be probable, proof of its existence is either very tenuous or is entirely lacking.

Among the dermatoses in the latter category are some of the eruptions caused by physical agents, which are the subject of this symposium. Probably nobody would disagree with the statement that some of the dermatoses that are discussed here are based on a peculiar hypersensitivity of the skin of the affected individual to certain physical agents. The clinical events themselves prove that these patients are more sensitive,

i.e., more capable of reacting, than other people living in the same community at the same time under approximately identical conditions.[8] However, the salient point is whether we are dealing with an *allergic* hypersensitivity that is based on a *specifically acquired* alteration in the capacity to react, as, for example in allergic eczematous, urticarial or tuberculin-type hypersensitivity, or *whether we are dealing here with* nonspecific nonallergic mechanisms, such as a primary irritant, photodynamic, phototoxic[4] or other reaction. As Epstein has stated, these primary irritant *and other nonallergic sensitization reactions due to* physical agents, just as primary irritant reactions due to chemical agents, apply indiscriminately to *all* individuals. Generally their intensity is in direct proportion to their dosage.

It has been known for many years that the skin of human beings deliberately can be made hypersensitive to light by intracutaneous or systemic administration of rose bengal and certain other agents. The urticarial *hypersensitivity engendered by rose bengal is* based on the photodynamic action of this substance, and not on a specific allergic sensitization. Yet the urticarial lesion produced can no more be differentiated from an allergic urticarial lesion on clinical or histologic grounds alone than can an urticarial skin reaction due to allergy to a food be distinguished from one due to a primary urticariogenic agent such as histamine.

At present this question may appear to be of more theoretic than practical interest. However, it has important practical implications, since the measures that must be taken for prevention and management are likely to differ *in many instances, depending on the*

mechanism that underlies the particular dermatosis Moreover, as knowledge in the field of immunology advances, it appears quite possible that in the not too distant future means will be developed for prevention of sensitization and for hyposensitization and desensitization that can be applied in those cases based on an allergic mechanism

In this introductory article I shall survey those features that can be utilized in attempts to differentiate allergic and nonallergic cutaneous hypersensitivity to physical agents Even though the other authors in this symposium may not agree with my concepts in every single detail, their statements regarding the allergic or the nonallergic nature of the various clinical syndromes will be based largely on similar considerations

Before listing the phenomena that suggest an allergic mechanism, I shall digress and mention one of the many fascinating questions in this field, i e., what are the actual allergenic substances in cases of allergic hypersensitivity to physical agents? It is hardly conceivable that the demonstrated or the presumptive antibodies in the sensitized cells could react with the physical agent itself, such as the radiant energy of a given wavelength, or with friction or cold Rather, it must be assumed that intermediary substances are involved in these reactions Indeed, the most acceptable theory that first was advanced by J Jadassohn [5] is that the physical agent such as cold or light causes the formation or the release of substances in the skin that have a damaging effect upon it. Later on Bernstein [1] and others applied this concept to allergic eruptions produced by physical agents and suggested that the actual allergen in these cases was a

metabolite in the skin. This sometimes is referred to as a "secondary allergen." Following the suggestion of S. Epstein,[2] Sulzberger and I[3] have postulated that there is good reason to suspect that the metabolite concerned is often, and perhaps always, a substance that occurs *normally* in human skin whenever it is exposed to the particular physical stimulus, and that only in certain susceptible individuals does this metabolite *act as an allergen.*

Perhaps this substance exists preformed in the skin and simply is released upon exposure to the physical stimulus. A second possibility is that it is newly formed after such exposure from a pre-existing substance, i.e., that we are dealing with conversion of a proantigen into the antigen.

If the hypothesis of an allergenic yet physiologic *metabolite proves to be correct, allergic hypersensitivity* to the physical agent does not occur, because the patient's skin elaborates a pathologic substance upon exposure to the physical agent Rather it develops because the patient is unusual in the sense that *he has the capacity to become allergic to a metabolite occurring in normal skin to which millions* of other human beings fail to develop an allergic response, although all of them elaborate the same metabolite upon exposure to the same physical agent There is much support, especially from passive transfer tests, for the assumption that the actual allergen is a normal rather than a pathologic metabolite, at least in some types of allergic hypersensitivity to physical agents. Take for example the circumstances that led us to formulate the hypothesis described above blood serum containing passive transfer antibodies against light from a patient with urticaria due to light

is injected intracutaneously in ten normal recipients Subsequently an urticarial response can be elicited in the injected sites in all ten recipients by exposing these sites to light It would be hard to understand why the urticarial reaction could be elicited regularly in all normal recipients unless the actual allergen was a normal metabolite that was released in all normal skins upon exposure to light There is another possible hypothesis, but it is one for which thus far there is little supporting evidence This hypothesis states that in cases where passive transfer of hypersensitivity to light, cold, etc, is possible the serum of the patients contains not only the sensitizing antibodies but also a proantigen which upon exposure to the physical agent is transformed into the actual antigen. For example, Epstein[4] maintains that certain observations made by him can be explained by the assumption that the serum from certain patients who had prurigo aestivalis contained *both* passive transfer antibodies plus a pro antigen

Still another explanation was proposed by Rajka,[7] who reviewed these problems in a comprehensive and critical fashion According to his "theory of reagin activation," the physical agent acts specifically upon a preformed substance, called a proreagin, and activates this into the reagin The activated reagin in turn acts as a catalyzer or organic enzyme and causes the sudden release of H substances, which bring about the clinically visible phenomena.

While there is no irrefutable and conclusive proof of any of these theories, I believe that as of the present time the theory supported by Sulzberger and me—according to which the actual allergen in physical allergies usually is a normal metabolite, present in all

metabolite in the skin. This sometimes is referred to as a "secondary allergen." Following the suggestion of S. Epstein,[2] Sulzberger and I [9] have postulated that there is good reason to suspect that the metabolite concerned is often, and perhaps always, a substance that occurs *normally* in human skin whenever it is exposed to the particular physical stimulus, and that only in certain susceptible individuals does this metabolite act as an allergen.

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sensitizations to certain contact and drug allergens in man.

The following are the most important criteria among those that are useful, in at least some forms of allergic hypersensitivity to physical agents, in supporting the concept of an allergic causal mechanism:

1. The demonstration of specific antibodies through passive transfer or other tests Examples are the passive transfer antibodies that often have been found in the blood serum of patients with urticaria due to cold and light Also reverse passive transfer tests and elicitation of passive transfer reactions at a distance from the site of exposure to the physical agent.

2. The demonstration of an incubation period of sensitization subsequent to which the clinical lesions and the skin test reactions can be elicited after a shortened interval, the so-called reaction time An example is the photo-allergic reaction to sulfonamides first described by Stephan Epstein[3]

3 The resemblance of the morphe, the course and other characteristics of the eruption to other dermatoses that have been proved to be based on an allergic mechanism An example is urticaria due to light (4000–5000 A), which, except for the absence of passive transfer antibodies in most cases,* in all *other* respects resembles urticaria due to light (< 3700 A), for which the concept of an allergic etiology has been supported through fairly regular demonstration of specific *antibodies*

4 Cutaneous or noncutaneous phenomena known to be associated with allergic diseases and occurring

* Exceptions to the usual absence of passive transfer antibodies in urticaria solaris (4000–5000 A) have been reported by Rajka[7] and Kesten[8]

normal skins upon exposure to the particular physical agent—still remains the most reasonable explanation of the majority of cases.

What are the criteria that aid in differentiating allergic and nonallergic hypersensitivities to physical agents? In general, one attempts to apply the *same criteria* as those that have been used to differentiate allergic and nonallergic hypersensitivities to other allergens. The following three points, according to Sulzberger,[8] must be fulfilled in order to establish the allergic nature of a reaction:

1. The causal agent was encountered at some previous time.
2. *The demonstrated alteration in the capacity to* react to the causal agent was the result of such previous encounter.
3. The response to the causal agent at the subsequent reaction-eliciting encounter was different from that which was produced at the first encounter.

Among the characteristic allergic phenomena that are helpful in establishing these three cardinal points are an incubation period followed by the much shorter reaction time, a specific spontaneous flare-up phenomenon, specific skin test reactions, specific antibodies, etc. Often it is not possible in hypersensitivities to physical agents to prove the existence of these and other criteria that characterize allergic phenomena. This is due partly to the fact that, for obvious reasons, deliberate experimental sensitizations in man usually are not permissible and feasible in studies on allergic sensitizations to physical agents. It is these experiments that have permitted beautiful demonstration of the various characteristic allergic phenomena in

sensitizations to certain contact and drug allergens in man

The following are the most important criteria among those that are useful, in at least some forms of allergic hypersensitivity to physical agents, in supporting the concept of an allergic causal mechanism:

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* Exceptions to the usual absence of passive transfer antibodies in urticaria solaris (4000–5000 Å) have been reported by Rajka[7] and Kesten[8]

in conjunction with the skin manifestations Examples are anaphylactoid reactions, angioneurotic edema bronchial asthma, etc., associated with cold urticaria

5. The clinical lesion, not one that is elicited normally by the particular physical stimulus, but one that is known to occur as an allergic eruption due to other agents. An example is eczema solare; sunlight *normally is incapable of eliciting a true eczematous* response, but lesions that *resemble very closely* those seen in eczema solare are observed very commonly as an allergic response produced by eczematogenic contact allergens Therefore, it is reasonable at least to suspect that eczema solare may be an allergic eruption

Among the dermatoses that my colleagues in this symposium will discuss are some for which an underlying allergic mechanism appears to be established beyond a reasonable doubt. In certain others among these dermatoses, the role of an allergic mechanism will be suggested by certain features, but unequivocal proof still is lacking. In still others, it will be apparent that an allergic mechanism, on the basis of all *evidence available at present, is unlikely. It is the* criteria that I have just listed that can be applied to each variety of hypersensitivity to physical agents in attempts to arrive at a differentiation of allergic and nonallergic mechanisms.

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2

Hypersensitivity to Trauma

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IN A BROAD SENSE we see clinically increased or abnormal reactivity of the skin to trauma or mechanical stimuli such as scratching, stroking, pinching, stretching, hitting, slapping or rubbing, or pressure in a wide variety of conditions, and it can be manifested in a number of ways. Some of the possible general ways in which such increased sensitivity may show itself can be listed as follows:

1. Dermographism, of the red, the white or the urticarial variety, and as special subtypes of the last mentioned, the dermographic prurigo described by Marcussen[a] and the kinds of mechanically induced local urtication seen in urticaria pigmentosa and at sites of old insect bites.
2. Blister formation, as illustrated by epidermolysis bullosa and in some of the porphyrias and, in a special sense, by the Nikolsky phenomenon in pemphigus.
3. Lichenification, as occurs in atopic dermatitis or dry neurodermatitis, in chronic contact eczemas and in lymphoblastomas.
4. Purpura, as, for example, in thrombocytopenic disorders.

most of my initial list of types of hypersensitivities to mechanical stimuli are excluded readily from being allergic responses to products or metabolites arising in direct consequence of such stimuli. However, there remain some cases of urticarial dermographism in which the evidence seems to be in favor of their having such a true allergic nature. Although the evidence is not absolutely conclusive, it is at least as good as the evidence supporting the allergic nature of other types of so called physical allergies. Also, I will consider briefly the situation in regard to the possible physical allergic nature of lichenification, not because there is any good evidence for considering it as an allergy to mechanical stimuli, but rather because we have no absolute reason for excluding this possibility.

In considering urticarial dermographism,[2, 6, 13] which sometimes is called urticaria factitia, we have to differentiate it, on the one hand, from pressure urticaria,[5, 13] and on the other, from the normal physiologic whealing response to violent mechanical stimuli such as is produced by a whiplash. Urticarial dermographism appears in a few minutes following relatively gentle and superficial mechanical stimuli such as the stroking of the skin. It is manifested usually by pruritic, typically histaminic, wheals, generally limited sharply to the areas of stimulation and surrounded by axon reflex flares of vasodilatation.

By way of contrast, pressure urticaria develops only after a latent period of several hours to a day, and only at sites of relatively intense and persistent pressure such as the buttocks and the soles. In such pressure urticaria, it almost seems as though the pressure brings about localized concentration of some etiologic

5. Hyperkeratinization, as seen in individuals in whom callosities form on the feet and the hands with exceptional ease.

6. Hyperesthesia or pain, as in herpes zoster, various neurologic disorders, and in all varieties of tender lesions from furuncles to leiomyomas and glomus tumors.

7. The kind of epidermal fragility (readiness to break down from traumatization such as scratching) seen in infantile eczema and in all types of acute and subacute eczematous dermatitis

And, finally, we might even include in this list,

8. The special kind of excessive wounding that occurs in Ehlers-Danlos syndrome.

It is evident from this list that hypersensitivity or increased or unusual reactivity of the skin to mechanical stimuli occurs very commonly and frequently has much clinical diagnostic value. However, in this symposium we are concerned only with *allergic* types of such hypersensitivity to mechanical stimuli, and so our first task is to decide which of these types of hypersensitivity, if any, can be considered to be truly allergic In order to do this, I wish again to call attention to the elementary definition of allergy already cited in this symposium by Baer, i e, that allergy is an acquired, specific alteration in the capacity to react, and, furthermore, as has been stated so often by Rostenberg,[11] that this must be based on an antigen antibody reaction It is of the greatest importance to keep clearly in mind this strict limiting definition if we are to avoid confusion about the role of allergy in various conditions

By applying this definition and the additional criteria presented in the introductory chapter by Baer,

mechanical stimuli. However, the question remains as to what proportion, if any, of these 5 per cent have some unique, possibly allergic, mechanism behind their hypersensitivity rather than simply a low threshold to the normal physiologic mechanisms of histamine release and action in response to trauma. Clinical observations pertaining to this subject have yielded variable information and also, incidentally, have given rise to the probably erroneous concept that acute or chronic urticaria is associated commonly with urticarial dermographism. Thus, claims are recorded in the literature that anywhere from 6 to 100 per cent of patients with such common urticarias show associated dermographism[3, 4, 8, 14] The difficulties with many of these observations have been not only methodologic, in that often inadequate controls were used—few attempts were made to standardize the mechanical stimulus and often excessively strong stimuli were used—but also fundamentally that apparently the wide normal range of physiologic triple response reactivity to mechanical trauma merges gradually with the degree of reactivity seen in clinically symptomatic urticarial dermographism, which possibly may have a specific allergic basis.

Although one can conceive of many ways to standardize the mechanical stimulus, I have found that a variation of a simple, old, weight dragging procedure, consisting of mechanically drawing across the skin a 2 mm ball-like metal point that can be weighted in graduated fashion, is a fairly satisfactory procedure. With such a device, the patients whom I have tested with clinically annoying symptomatic urticarial dermographism all showed threshold whealing under a load of 200 Gm or less, whereas, in a series of 40 ap

factor carried in the blood stream by virtue of circulatory stasis.

The physiologic urticarial response to violent mechanical stimuli differs clinically from urticarial dermographism almost only in the vastly greater stimulus that is required to elicit the reaction, although ordinarily such intense stimuli give rise to painful, rather than simply itching, sensations. Despite this qualitative clinical similarity, the mechanism in physiologic whealing by which histamine liberation is triggered can, and possibly does, differ fundamentally from that operating in *true urticarial dermographism*

In considering these mechanisms I wish first to turn to the work of Sir Thomas Lewis,[7] who pioneered in detailed physiologic studies of cutaneous reactions to mechanical as well as other forms of injury and developed the classic H-substance liberation theory, by which we account for the end-mechanism in all varieties of urticarial reactions. In essence, his theory stated that a variety of injurious agents, including strong mechanical stimuli, when acting on the skin, cause the liberation of histamine or a histaminelike substance, which then produces the triple response consisting of (1) initial local vasodilatation, (2) wheal formation and (3) axon reflex erythematous flare Among physically injurious agents, he noted that intense cold stimuli, as well as violent mechanical stimuli, regularly produced this triple response However, in response to what he called "firm" stroking, no more than 5 per cent of his young normal subjects developed conspicuous whealing and axon-reflex flare in addition to the local vasodilatation Thus, it is apparent on the basis of his work that 5 per cent of the population have hypersensitive whealing responses to

mechanical stimuli. However, the question remains as to what proportion, if any, of these 5 per cent have some unique, possibly allergic, mechanism behind their hypersensitivity rather than simply a low threshold to the normal physiologic mechanisms of histamine release and action in response to trauma Clinical observations pertaining to this subject have yielded variable information and also, incidentally, have given rise to the probably erroneous concept that acute or chronic urticaria is associated commonly with urticarial dermographism Thus, claims are recorded in the literature that anywhere from 6 to 100 per cent of patients with such common urticarias show associated dermographism[3, 4, 9, 14] The difficulties with many of these observations have been not only methodologic, in that often inadequate controls were used—few attempts were made to standardize the mechanical stimulus and often excessively strong stimuli were used—but also fundamentally that apparently the wide normal range of physiologic triple response reactivity to mechanical trauma merges gradually with the degree of reactivity seen in clinically symptomatic urticarial dermographism, which possibly may have a specific allergic basis

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lack of association between such ordinary urticarias and urticarial hypersensitivity to mechanical stimulation

As regards passive transfer studies, recently I had the opportunity to carry out such tests with the sera of four patients who had annoyingly symptomatic urticarial dermographism with clearly high degrees of specific sensitivity to mechanical stimuli In three of these cases very clear-cut positive passive transfer results were obtained A number of years ago, Walzer [24] also noted positive passive transfer tests in seven out of 12 cases of urticarial dermographism that he studied, and Rothman [12] also has had a very high degree of success with such passive transfer tests

In regard to the clinical aspects of urticarial dermographism of the highly sensitive type, some noteworthy features are the following

The urticarial hypersensitivity is highly specific for mechanical stimuli only, and as a rule the whealing response is limited sharply to the areas of direct application of such stimuli Other physical modalities such as heat, cold or radiant energy fail to elicit the response, and, in general, no past history of urticaria, whether ascribable to emotional, specific, antigenic or unknown causes, can be obtained

The condition is an acquired one, developing usually to a maximum degree over a relatively short period of time often measured in days It may begin at almost any age after infancy and appears in both sexes

Duration of the disorder is unpredictable In some cases it appears to be permanent, in others it may last for almost any short or long period of time Often the severity of the condition shows marked spontaneous

parently normal individuals, this level of loading never caused whealing, although on boosting the load to 1000 Gm., which was rather painful, about 20 per cent of this normal series of individuals showed varying degrees of minimal to mild whealing. This latter finding is in agreement with the earlier observations of Lewis[7] and Walzer,[14] that in about one-fourth of normal individuals repeated or firm stroking of the skin is followed by some degree of detectable swelling. On the basis of these observations, I have found useful for purposes of classification an admittedly arbitrary line which divides those cases that respond with whealing to less than 200 Gm. from those that can be elicited only by greater pressures Generally, of course, the responses in clinically symptomatic patients fall into the first category

To return to the subject of the often claimed association of urticarial dermographism with the common kinds of acute and chronic urticaria, I do not believe that there is any such association, particularly if we consider only the highly sensitive types of urticarial dermographism In a number of patients with ordinary chronic as well as acute urticaria, even during periods when new lesions were erupting actively in response to active known antigenic stimuli, I have been unable to demonstrate any dermographism even with relatively intense, painful stroking A few years ago Fisher and Schwartz[3] found likewise that in response to firm stroking with a tongue blade the incidence of any degree of local whealing in a control series of patients with various dermatoses other than urticaria was 5 per cent, and that the similar incidence of such whealing in 100 patients with subacute or chronic urticarias was 6 per cent, thus indicating a

the other hand, we cannot exclude entirely in these cases of urticarial dermographism where passive transfer can be shown the possibility that the serum contains some nonantibody substance that simply lowers directly the physiologic threshold for histamine liberation induced by mechanical stimuli. In the case of mosquito bites, where repeated local urtication can be elicited by scratching sometimes for as long as a week, it would appear that some such nonantibody-sensitizing substance or mechanism actually is involved. Also, in urticaria pigmentosa a nonantibody mechanism obviously is involved in the ready urtication of the lesions in response to mechanical stimuli. Here, apparently, the sensitivity to such stimuli is based simply on a quantitative factor, i.e., that many more pressure-sensitive, very potent histamine-liberating, cells—the mast cells—are available to respond to mechanical stimulation than is the case in normal skin. From this viewpoint it might be of interest to investigate the mast-cell picture quantitatively in the 5 per cent of the normal population whom Lewis and others have found to have hypersensitive urticarial responses to less than the most violent mechanical stimuli.

To turn now to lichenification, we all recognize it as a very important and yet a far from understood dermatologic phenomenon. I believe that clinical observations suggest strongly that without mechanical stimuli lichenification could not develop or be sustained long. This is illustrated well by the involution of lichenification in lichen simplex chronicus after no therapy other than strict protection from mechanical stimuli. On the other hand, persistent mechanical stimuli alone need not lead necessarily to

fluctuations, which make interpretation of duration difficult.

Antihistamine drugs can be used with success to suppress symptoms.[1] Even iontophoresis of antihistamines into the skin has inhibited locally the whealing response,[10] thus tending to support the final histaminic step in the pathogenesis of the disorder.

Finally, it is often possible locally to exhaust reactivity temporarily by frequent vigorous mechanical stimulation of the same area. This local exhaustion phenomenon may account for the frequently lesser reactivity of parts in these patients ordinarily exposed most extensively to mechanical stimuli such as the feet, the hands and the buttocks. Application of this exhaustion phenomenon also can be useful therapeutically at times, and in some cases symptomatic benefit can be obtained from daily vigorous extensive rubbing or scratching of the skin while in a hot bath. However, care must be taken in very highly sensitive cases not to cause such severe widespread reactions as to precipitate systemic histamine shock.

After considering all this information, and particularly on the basis of the acquired and the specific nature of the highly sensitive types of urticarial dermographism, the analogy of the lesions to those seen in truly allergic states and the clear demonstration of the passive transfer phenomenon by serum, one is tempted strongly to conclude that such urticarial dermographism represents a genuine *allergic* reaction to some product formed in the skin specifically in response to mechanical stimulation. Certainly it is easy to conceive of specific chemical alterations arising in tissues either directly or indirectly as the result of mechanical forces acting to disrupt structural relationships. On

the other hand, we cannot exclude entirely in these cases of urticarial dermographism where passive transfer can be shown the possibility that the serum contains some nonantibody substance that simply lowers directly the physiologic threshold for histamine liberation induced by mechanical stimuli. In the case of mosquito bites, where repeated local urtication can be elicited by scratching sometimes for as long as a week, it would appear that some such nonantibody sensitizing substance or mechanism actually is involved. Also, in urticaria pigmentosa a nonantibody mechanism obviously is involved in the ready urtication of the lesions in response to mechanical stimuli Here, apparently, the sensitivity to such stimuli is based simply on a quantitative factor, i e, that many more pressure-sensitive, very potent histamine liberating cells—the mast cells—are available to respond to mechanical stimulation than is the case in normal skin From this viewpoint it might be of interest to investigate the mast cell picture quantitatively in the 5 per cent of the normal population whom Lewis and others have found to have hypersensitive urticarial responses to less than the most violent mechanical stimuli

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lichenification. Thus, for example, in many cases of pruritus ani of long duration, even though there is ample evidence of scratching, lichenification may not develop. Also, the sharply circumscribed, circular nature of the lichenification seen at times in lichen simplex chronicus cannot be explained by scratching alone, since scratching never is done in such sharply delimited geometric fashion.

It is clear that some accessory factor besides rubbing or scratching is required for lichenification to appear. The nature of this accessory factor is not known, but certainly it is present in the conditions under which this change develops with unusual ease such as atopic dermatitis, chronic allergic or contact eczemas, and in lymphoblastomas such as Hodgkin's disease In connection with the latter, it is noteworthy that although generalized itching may be as severe in some cases of pruritus due to renal or liver disease as in the lymphomas, such a ready tendency toward lichenification is not seen so commonly.

Two features common to all conditions that show easy lichenification are persistent rubbing or scratching and the presence of chronic inflammatory round cell infiltrates in the involved areas Of course, it is tempting to speculate that somehow these chronic inflammatory cells bring in with them some factor that conditions the skin to lichenify in response to some product liberated by mechanical stimuli Furthermore, it may not be too far fetched to suppose that actually in some cases such a hypothetic lichenification-conditioning factor may be a specific antibody carried by those cells against some product arising in response to mechanical stimuli. Of course, serum passive transfer would not be demonstrable in such a

mechanism in the same way that such transfer is not demonstrable in allergic eczematous contact dermatitis However, without some definite experimental evidence such pure speculation perhaps is meaningless Nevertheless, it does bring out that theoretically in some cases at least lichenification can be looked upon as a specific allergy to some product arising in response to mechanical stimuli in which antibodies would be of the cellular type, as in the eczematous or the delayed types of allergic reactions.

SUMMARY

In summary, a list has been presented of the many general ways in which hypersensitivity to mechanical stimuli can manifest itself On the basis of a strict limiting definition of allergy, most of these manifestations, with the possible exceptions of some cases of urticarial dermographism and lichenification, obviously were not physical allergies

The clinical features of urticarial dermographism were reviewed, as were the problems of its differentiation from pressure urticaria and physiologic whealing in response to violent mechanical stimuli. The need for standardization and control of testing procedures in attempting the latter differentiation was pointed out especially since, in degree, there seems to be a gradual merging and overlapping of the reactions seen in urticarial dermographism with those seen in physiologic whealing

In the very sensitive types of urticarial dermographism successful serum passive transfer can be demonstrated in the majority of cases In these cases the urticarial reactions are highly specific for mechanical

stimuli, and as a rule there is no association with chronic or specific urticarias of other types.

On the basis of its acquired, specific nature, its close resemblance to known allergic types of reactions, and the positive passive transfer studies, it was possible to view urticarial dermographism as an allergy to some product arising in the skin in response to mechanical stimuli. However, the possibility could not be excluded that the condition might be based on some circulating nonantibody substance that simply lowers the physiologic threshold for histamine liberation in response to mechanical stimulation.

Finally, lichenification was discussed briefly from the purely speculative viewpoint, that in some cases it might represent possibly an allergy to some product arising in response to mechanical stimuli in which antibodies would be of the cellular type as occur in eczematous or delayed types of allergic reactions.

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3

Eczematous and Polymorphous Hypersensitivity to Light

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INTRODUCTION

THE DIRECT EFFECTS of light upon the skin are of two kinds (a) specific effects initiated by a photochemical reaction and (b) nonspecific or "radiant heat" effects that result from a local rise in temperature and may cause a thermal burn. The photochemical reaction results from the activation of molecules in the tissues by energy from the light absorbed The effective wavelengths of light are designated as the "action spectrum" concerned in the reaction To determine the action spectrum involved in producing a dermal reaction is important, because it corresponds closely to the absorption spectrum of the substance responsible for the reaction and may give a clue as to its identity

Sunburn is a normal response of the skin to overexposure to light with direct injury to the cells of the prickle cell layer of the epidermis The injured cells release substances that cause the erythema, edema,

pighian layer and the stratum corneum thicken normally in response to exposure to light.

Theoretically, dermatitis following exposure to light may result from many possible disturbances in the skin. Among them: (1) from formation or release of more than usual amounts of normal metabolites with a consequent exaggeration of the normal response (sunburn), (2) from formation or release of normal metabolites with an abnormal (allergic) reaction to these metabolites, (3) from formation or release of abnormal metabolites with resulting direct irritation; (4) from formation or release of abnormal metabolites with an allergic response to them. Epstein[16] uses the terms *phototoxic* or *photo-allergic* to characterize these skin reactions to light.

Theoretically, with wavelengths shorter than 3300 A any of the above reactions could result with or without the intervention of photosensitizing agents. With wavelengths longer than this any of the above could develop if a photosensitizer having an appropriate absorption spectrum was concerned and if intensity and duration of exposure were sufficient.

One of the ways in which an atom or a molecule may dissipate the energy acquired by absorbing light is by fluorescence, i.e., emitting further radiation. The wavelength of light emitted usually is longer than that absorbed. Theoretically, this new or secondary radiation could exert an additional biologic effect perhaps involving a different photosensitizer.

Photosensitizing agents, whether they are chemicals, such as drugs or coal tar derivatives, or plant products, may reach the skin either by contact or by ingestion or injection. Endogenous substances, such as abnormal metabolites or toxins or other products absorbed

vesiculation, scaling and pigmentation that characterize this reaction. The sunburn-action spectrum extends from below 2500 Å to 3200 Å with a peak at about 2970 Å. The wavelengths of sunlight as it reaches the earth extend from approximately 2900 Å to 18,500 Å.[2]

In general, direct destructive effects of light in the skin are produced only by wavelengths shorter than about 3300 Å. This may be due in part to the greater energy of the quanta of light of shorter wavelengths. Probably also it is due to the fact that protein and nucleic acid, two important compounds in cells and cell nuclei, absorb light strongly in the spectral regions below 3300 Å but not appreciably at longer wavelengths.

Normal individuals vary greatly in their sensitivity to sunlight. Blondes are more sensitive than brunettes, but pigmentation is not necessarily the most important determining factor. In white-skinned individuals the melanin pigment normally is located chiefly in the cells of the basal cell layer. In this location it can offer little protection against the damage of the sunburn spectrum to the prickle cells. Following exposure to sunlight, about the time sun tan first appears, melanin begins to migrate into the more superficial layers, eventually reaching the stratum corneum. This is followed by the production of new melanin by the dendritic melanoblasts in the basal cell layers of the epidermis.[3]

The thickness of the epidermis, especially of the stratum corneum, is of greater importance. The individual keratin flakes strongly diffuse or scatter the shorter ultraviolet waves, and the protein in the keratin absorbs light of this wavelength. Both the mal

pighian layer and the stratum corneum thicken normally in response to exposure to light.

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Photosensitizing agents, whether they are chemicals, such as drugs or coal tar derivatives, or plant products, may reach the skin either by contact or by ingestion or injection. Endogenous substances, such as abnormal metabolites or toxins or other products absorbed

from foci of infection, also may act as photosensitizers Presumably the only requirements of such a substance would be that it combine with some vulnerable tissue fraction *within the range of penetration of light and* be able to absorb this light. When such a photosensitizing chemical absorbs light, energy is released and, if sufficiently intense, results in damage to the tissues *to which it is attached.*

A particular type of photosensitization, given the name *photodynamic action,* involves sensitization of tissues by a wide variety of dyes or natural pigments. On adequate exposure to light of a wavelength capable of being absorbed by the sensitizing agent, oxidation of readily oxidizable substances in the photosensitized tissues occurs with the uptake of oxygen The photosensitizing agent transfers energy from the absorbed light to the reaction without itself being changed[2] Here again, the substances released by tissues damaged by this photochemical reaction may act as direct irritants or as antigens to which the patient may be specifically allergic

Kesten and Slatkin,[24] Stokes, Beerman and Ingraham[25] and others list numerous substances that have been reported as acting as photosensitizers Among the chemicals that act as intermediate light absorbers when used internally are a number of little used drugs such as *eosin, erythrosin, fluorescein, methylene blue,* rose bengal and acriflavine Among the drugs more commonly used, the sulfonamides, the barbiturates and quinine are listed Gold and arsphenamine also are included.

Among the chemicals that act as sensitizers when applied to the skin are again various dyes, coal tar and coal tar derivatives, including creosote, sulfon

amides and, rarely, salts of para-aminobenzoic acid. A number of different plants and plant extracts are known to act as contact photosensitizers Berlock dermatitis associated with the application of cologne waters, perfumes, bergamot oil and citron oil fall into this group

TYPES OF REACTION

Considering the variety of mechanisms that may be involved and the variability of tissue response, especially when an allergic mechanism may be involved at times, it is not surprising that the skin reactions to light may be truly polymorphous

Classifications of diseases caused by light have been proposed by Hausmann and Haxthausen,[21] Lamb, Shelmire, Cooper, Morgan and Keaty,[24] Kesten and Slatkin[22] and others Polymorphous light-sensitive eruptions are not well defined In this group one apparently may include eruptions with the characteristics of (1) erythema with or without edema, (2) erythema multiforme, (3) eczema, (4) papular urticaria or prurigo and (5) chronic inflammatory plaquelike dermatitis Many cases may show combinations of these varying types of lesions

Occasionally a patient may experience discomfort and itching of the skin following exposure to sunlight although no definite eruption is evident More prolonged or repeated exposure may result in visible signs of dermatitis

Transient erythematous eruptions of the face and the neck may appear within a few moments after exposure to light and consist of simple erythema or of erythema and edema, they disappear without trace after an interval of minutes or an hour or two. I

know of one such case in a woman who could not tolerate even two or three minutes of bright sunlight on her face or the sides and the back of her neck without developing a bright, blotchy erythema in these areas Sunlight filtered through window glass did not provoke her eruption.

Erythema multiformelike eruptions (erythema solare perstans) perhaps are seen more commonly. In these, erythematous maculopapular areas appear usually over the nose, the malar areas and elsewhere on the face and the neck. The lesions usually are discrete, but they may become confluent and cover large areas. Differentiation from the early erythematous form of lupus erythematosus may be difficult The absence of systemic symptoms and abnormal laboratory findings and the disappearance without sequelae help to distinguish this from lupus erythematosus Cahn, Levy, Shaffer and Beerman[6,7] suggest that, in reality, many polymorphous light eruptions are subclinical manifestations of systemic lupus erythematosus.

Eczematization with redness, some degree of edema and infiltration and papular or papulovesicular change is most common in our experience Secondary changes, including scaling, excoriation, weeping and crusting, may occur

Prurigo aestivalis begins with an erythematous, pruriginolike papular or papulo urticarial eruption It is seen more commonly in adults than in children Itching leads to excoriation and to infiltration and lichenification. Varying degrees of secondary eczematization may occur. Apparently prurigo aestivalis is a common type of solar dermatitis, at least in certain parts

of the United States of America. Cahn, Levy and Shaffer[6] report 16 cases of this type followed at one time

Lamb *et al*[24] have emphasized a plaquelike type of solar dermatitis. The plaques vary from 2 to 5 cm in diameter and occur most commonly on the cheeks, the sides of the neck or the exposed "V" of the upper anterior chest. They are described as pinkish in color in contrast with the tanned hyperpigmented surrounding skin. They are indurated and may show telangiectasia, excoriation, lichenification and scaling. Apparently they may develop by confluence of earlier papular or eczematous lesions. Lamb *et al*[24] report this type of lesion in 19 of 34 patients of solar dermatitis studied by them. Perhaps the more prolonged and intense exposure in the southwestern part of the United States, where this series of cases was observed, accounts for the frequency of this type of reaction.

Michelson[25] would class the vesicular and the vesiculobullous types of solar dermatitis now described as hydroa aestivale or hydroa vacciniforme simply as vesicular or bullous light-sensitive dermatitis, provided no disturbance in porphyrin metabolism could be shown to be present. Hydroa aestivale is characterized by the appearance of crops of vesicles on an erythematous macular base. The vesicles may rupture or become umbilicated and dry, leaving crusted lesions that heal slowly and often are followed by a superficial scar. If severe, these cases may show hemorrhagic and ulcerative lesions and heal with marked scarring, atrophy, sclerodermalike sequelae and deformity. Attacks usually appear during early childhood. Adults are affected less commonly, many cases

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porphyrins This should be done preferably during an acute attack

It has been shown that hematoporphyrin injected intradermally will sensitize the skin so that exposure to light results regularly in the appearance of an itching wheal and surrounding flare. The absorption spectrum of the various porphyrins lies between 3000 A and 6500 A. Photosensitization by the porphyrins is produced *principally* by wavelengths between 3000 A and 4500 A [2]

It has not been possible routinely to reproduce experimentally vesicular or polymorphous eruptions by the injection of porphyrins followed by exposure to light Blum and Pace [4] may have done so in one patient Many patients with porphyria have no skin lesions Thus, although porphyria and polymorphic eruptions provoked by light may occur in the same patient, the relationship between the two is not understood clearly

In most cases of pellagra, exposure to sunlight is important in precipitating and localizing the dermatitis Both the skin lesions and the constitutional symptoms may be flared by exposure to light However, this is not always true, and in some patients skin lesions occur on both exposed and covered areas and appear to be independent of exposure to light. Heat as well as light may provoke the appearance of the dermatitis

Photosensitivity in pellagra is reviewed extensively by Stokes, Beerman and Ingraham [39] Kesten and Slatkin regard the localization of the skin lesions in pellagra on the exposed areas as a Koebner phenomenon with light as the source of irritation [22]

Disturbed porphyrin metabolism cannot be demonstrated regularly in pellagra

tending to clear during early adolescence. Itching is less common than burning and stinging. No particular spectral region has been shown to be responsible, varying wavelengths apparently precipitating attacks in different individuals. Exposure to wind and heat, as well as to light, is said to precipitate attacks occasionally.

If studies reveal porphyria, Michelson [27] would classify the case as one of porphyria with skin lesions described morphologically.

In the rare cases of congenital or erythropoietic porphyria the patients are markedly sensitive to sunlight. *The skin lesions are bullous and appear on the exposed areas, especially the face and the hands.* Repeated crops of lesions, together with secondary infection, lead *to scarring and at times to severe mutilation.* Hyperpigmentation is present. It is in this form of porphyria that urine the color of port wine is seen regularly.

The skin lesions in the cutanea tarda type of hepatic porphyria, and occasionally in the mixed or combined type, are not uniform in appearance. Papular or papulovesicular lesions with excoriation and eczematization are common. Pronounced tanning or grayish-brown hyperpigmentation often is seen. The skin lesions are not limited *always* to areas exposed to light, although they are seen predominantly on the exposed areas. Unusual heat, trauma and other factors may *provoke flares. Men are affected more often* than women, and most often in the fifth and the sixth decades of life. Liver damage, frequently associated with alcoholism, is present.

Since the skin lesions alone are not diagnostic, *all* patients with idiopathic polymorphous light-sensitive dermatoses should have urine specimens screened for

porphyrins. This should be done preferably during an acute attack

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The skin lesions in the cutanea tarda type of hepatic porphyria, and occasionally in the mixed or combined type, are not uniform in appearance. Papular or papulovesicular lesions with excoriation and eczematization are common. Pronounced tanning or grayish-brown hyperpigmentation often is seen. The skin lesions are not limited always to areas exposed to light, although they are seen predominantly on the exposed areas. Unusual heat, trauma and other factors may provoke flares. Men are affected more often than women, and most often in the fifth and the sixth decades of life. Liver damage, frequently associated with alcoholism, is present.

Since the skin lesions alone are not diagnostic, all patients with idiopathic polymorphous light-sensitive dermatoses should have urine specimens screened for

weather and less than normal outdoor exposure.

In contrast with urticarial reactions to light, in which the eruption frequently develops promptly after exposure, eczematous and polymorphic eruptions may be insidious and delayed. In the milder forms particularly, clear-cut flares may not be noted following individual exposures, and the reaction may appear to be cumulative.

Confusion may arise from the fact that water vapor does not absorb as much of the ultraviolet light as it does visible light and the longer infrared. Thus, the sky radiation reaching us on a hazy or a cloudy day may be a relatively potent source of ultraviolet light and lead to sunburn or other types of solar dermatitis when these wavelengths are concerned.

By far the greatest help to me in the diagnosis of solar dermatitis is the localization of the eruption.

When some photosensitizing agent that reaches the skin by contact is involved, the location of the eruption will depend on the areas of skin that are contaminated by the substance. When external contact factors are not involved, the pattern usually is more uniform.

Involvement of the hands is confined to the backs of the hands and the fingers. The opposing sides of the fingers are free of eruption. The skin over the distal phalanges may not be involved. The interdigital webs usually are clear, or at most only the more open dorsal portions are involved, and the eruption fades in the deeper interdigital areas.

The dermatitis is present on the radial and the lateral aspects of the wrists and the forearms, whereas the volar and the ulnar sides are free. On the arms it is usually only the lateral surface that shows the

DIAGNOSIS

The morphology of the dermatitis alone cannot be expected to be the determining factor in the diagnosis of solar dermatitis. History may be helpful. However, the virtues of sunlight are acknowledged so widely that it is difficult for some patients to realize that exposure to light may be harmful. Once this possibility is realized, the patient may be able in retrospect to associate his dermatitis with exposure to light. Of course, people whose work or recreation takes them out of doors are affected more often. Exposure to artificial light has been reported as causing trouble in rare instances.[5]

One may determine that the eruption recurs in the spring and the early summer, lessens in intensity in the fall and may clear during the winter. This may be because the ozone in the earth's atmosphere absorbs more strongly the shorter ultraviolet rays than the longer ultraviolet and visible light. Thus, the winter sun traveling a longer diagonal path through the earth's atmosphere loses much of its ultraviolet light. The skin also may develop gradually some increased resistance to light as the summer advances and again lose this during the winter months when light is weaker and exposure less frequent. In some, whose sensitivity is marked, and in parts of the world where winter weather is clear and bright, solar dermatitis may persist throughout the year.

Patients may volunteer that flares have occurred during periods of unusually bright and sunny weather or following unusual exposure to light (swimming, fishing, boating, skiing). Likewise, remissions may have been noted to follow periods of heavily overcast

whose neckwear is less uniform. In both men and women, the exposed "V" of the upper anterior chest may be involved when open shirts or dresses are worn.

Only occasionally will the upper surface of the feet and the anterior surface of the lower part of the legs be involved.

These features of localization are not always clear cut. Autosensitization dermatitis due to absorption from areas of primary involvement may appear in areas of skin not exposed to light. At times this may be widespread and confusing.

ACTION SPECTRA

In the eczematous and the polymorphic type of sensitivity to light, the reaction is produced most often by light in the sunburn spectrum. In the cases studied by Blum, wavelengths shorter than 3150 A were required.[2]

Epstein[14] reports cases of prurigo aestivalis in which the eruption was provoked by exposure to ultraviolet light and also by exposure to alpha rays from thorium X. He concludes that this phenomenon is not dependent on sunburn radiation but follows a marked radiation erythema, irrespective of the wavelengths that produce it.

In determining the wavelengths (action spectrum) involved light from different generators may be helpful.

None of the therapeutic lamps commonly available produces light restricted altogether to a particular spectral zone. For example, the so-called cold quartz lamp, with a quartz burner containing neon and mercury vapor and operated with low vapor pressure, low

eruption, and most often only the distal portion that is exposed below short sleeves.

The eruption usually is most marked on the lower portion of the forehead, the nose, the cheeks and the *sides and the back of the neck. The areas close to* the hairline often are spared, especially in women. In men who wear a hat habitually the forehead may be free of eruption, or it may appear only on the prominent supra-orbital areas. The eyelids usually are spared. In those whose globes are slightly exophthalmic a small area on the upper lid most exposed to light may be inflamed. In those who do not wear hats and whose hair is short, the rim, the lobe and the "exposed" portions of the pinna of the ears may *be involved noticeably. The recessed anterior por-*tions of the shell and the areas behind the lobe and beneath the ear are free of eruption. When the upper part of the pinna is protected by hair or hats, only the lower part of the ear and the ear lobes may show the reaction.

The upper lip directly beneath the nose usually is clear, and the transverse sulcus between the lower lip and the chin is relatively free, while the prominences of the sides and the front of the chin often show a marked *eruption. The exposed mucosal surface of* the lower lip may be involved, while the opposing surface of the upper lip is free. The submental region rarely is affected.

Occasionally the left upper extremity and the left side of the face and the neck may be broken out more intensely than the right due to exposure of these areas while driving an automobile.

In men the eruption frequently stops sharply at the collar line. This may not be so striking in women,

whose neckwear is less uniform. In both men and women, the exposed "V" of the upper anterior chest may be involved when open shirts or dresses are worn.

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Most of the cases of contact photodermatitis, such as those reported by Sams[44] in which lime oil, cologne and toilet water act as photosensitizers, are examples of phototoxic reactions. Likewise, most of the dermatoses involving photodynamic action are examples of direct irritation by the metabolites produced *or* released in the reaction, whether the sensitizer is endogenous or exogenous. However, an allergic response always is possible, provided that the exposures are sufficiently intense and frequent and the patient has a sufficient "allergic potential." The *occasional* delayed reactions reported by Epstein and Blum following injection of sulfanilamide,[2, 12] by Blum following injection of hematoporphyrin,[2] and by Sams following application of lime oil and subsequent exposure to light[44] apparently are examples of *delayed* photoallergic responses superimposed on phototoxic ones.

It is probable that *many*, *if not all*, of the eczematous and the polymorphous eruptions due to light involve an allergic response, although there are relatively few reports of cases *in* which adequate proof based on the criteria reviewed in this symposium by Baer has been presented.

The character of the eruption in eczema solare suggests that of allergic *contact* dermatitis. Likewise, the eruptions *of* prurigo aestivalis and the vesicular types of solar dermatitis *in* evolution and behavior, as well as appearance, suggest an *allergic* response rather than one of primary irritation.

Epstein[16] presents evidence that prurigo aestivalis is an allergic response. He notes that the incubation period is in favor of an allergic mechanism. Alternating phases of sensitivity and desensitization suggest the exhaustion of antibodies *in* an allergic reaction

line at 254 millimicrons and much less intense at 297 and 313. It also emits small amounts of light in the longer ultraviolet and visible spectra. The ordinary quartz mercury arc lamp operated at low voltage and a relatively high amperage generates a relatively high temperature and vapor pressure, emits 28 per cent total ultraviolet, 20 per cent visible and 52 per cent infrared radiation[9, 10]

The radiation produced by the carbon arc varies with the type of carbon electrodes used but also includes light from the shorter ultraviolet to infrared

With sunlight or light generators normally available, it is necessary to use glass filters that transmit only light of certain wavelengths interposed between the light source and the skin sites to be tested

Ultraviolet light below 3200 A will not pass through ordinary window glass A wide variety of special glass color filters can be obtained that will transmit only limited portions of the solar spectrum[11] Exposure to light through appropriate filters of this type often will allow the effective wavelengths to be determined fairly accurately.

MECHANISMS

The rare cases of transient erythema that appear shortly after exposure and clear quickly are almost certainly examples of direct irritation or phototoxic reactions. It is probable that unusually severe sunburnlike reactions also are examples of the same mechanism. The primary prompt (1–24 hours) erythematous reaction produced regularly at the site of injection of sulfanilamide[12] and hematoporphyrin[2] into normal skin and subsequently exposed to light belongs in this category.

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Epstein [26] presents evidence that prurigo aestivalis is an allergic response He notes that the incubation period is in favor of an allergic mechanism Alternating phases of sensitivity and desensitization suggest the exhaustion of antibodies in an allergic reaction

The phenomenon of provocation of lesions of prurigo aestivalis and of other light-sensitive dermatoses by heat and by irradiation with alpha and gamma rays is explained more easily via an allergic mechanism than a direct phototoxic effect.

One patient with contact eczematous type of solar dermatitis tested by Lamb *et al.*[24] with cold quartz light over an area 1 in in diameter on his back showed an intense pathologic sunburn reaction at the irradiated site. Seventy-two hours later an extensive exacerbation occurred on the face and the neck at the sites of previous solar dermatitis.

Seller and Liebner[35] reported four cases of prurigo aestivalis in which exposure of uninvolved skin to mercury arc radiation caused a normal sunburn response at the irradiated site but provoked a flare of prurigo lesions in areas of skin previously involved

These findings would indicate an allergic mechanism with the production or the release of a circulating antigen that combined with antibodies fixed to cells in the previously affected skin Sams has reported a group of cases of eczematous or papular or papulo-urticarial eruptions occurring in patients who had applied sunscreen agents followed by exposure to sunlight.[37] *In one such case application was made of* a solution of digalloyl trioleate and of a sunscreen cream containing this screening agent to an area of skin not previously exposed to light These areas then were exposed to light of sufficient intensity to provoke a first degree erythema in the unprotected skin surrounding the test sites. At the end of 24 hours nothing except the screening effect was noted. At the end of 36 hours itching began to develop in the test sites, and a papulo-urticarial eruption began at the edges

of the screening streaks. This increased in intensity during the next 5 days and then began to subside. The character of the eruption in the test sites and the delayed reaction time suggest that this is an allergic response and not a primary photochemical reaction.

Epstein [12] succeeded in passive transfer of sensitivity in two cases of prurigo aestivalis—and possibly in a third—out of six cases in which it was attempted. He reviews the subject of passive transfer of hypersensitivity to light. Stein [25] reported accomplishing this in a patient with hydroa vacciniforme.

Flarer [18] injected serum from the bullae in two cases of bullous reaction to light into the skin of three test subjects. Subsequent exposure to mercury arc radiation produced reddening and vesiculation. Injection of blood serum did not provoke this response.

Mukhin and Akobjan [20] injected blood serum from a patient with prurigo aestivalis into white rats. Subsequent mercury arc radiation resulted in excitement, pruritus, edema, conjunctivitis and even death.

Callaway [8] was able to sensitize the skin of normal individuals by injecting serum from a woman with light sensitivity. An exaggerated sunburn type of reaction resulted. The patient had increased amounts of coproporphyrin I in the urine. It is suggested that in Callaway's patient, and probably in some of the others, these reactions may represent transfer of a photosensitizing substance with the serum rather than transfer of antibodies in an allergic mechanism. Therefore, passive transfer of sensitivity in this situation is not always proof of an allergic reaction.

Using the classic Prausnitz-Kustner technic, passive transfer of a delayed allergic light sensitivity reaction apparently has been accomplished only rarely.

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One patient with contact eczematous type of solar dermatitis tested by Lamb *et al*[34] with cold quartz light over an area 4 in in diameter on his back showed an intense pathologic sunburn reaction at the irradiated site. Seventy-two hours later an extensive exacerbation occurred on the face and the neck at the sites of previous solar dermatitis

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doors are handicapped seriously by solar sensitivity. The most practical solution may be a change in work routine that enables them to work indoors. Occasionally night work can be substituted. Indoor work may be injurious to those sensitive to ultraviolet light if interior lighting with fluorescent lights is used, unless the ultraviolet part is screened out by an appropriate glass enclosure.[5]

LIGHT-SCREENING AGENTS

Local applications that contain sufficient pigment to absorb or to reflect light may give adequate protection. The rather conspicuous application of zinc oxide ointment that youngsters apply to their sunburned noses does quite well at the beach but would hardly be suitable in town. Such cosmetic preparations as Covermark can be effective.

There are a great many "sunscreen" lotions and creams available that contain preparations that absorb the shorter wavelengths of light. Kesten and Slatkin[2] list a number of these and report their relative value. They confirm the earlier findings of Rothman and his co-workers[21, 22] that ointments or creams containing 15 per cent para-aminobenzoic acid offer excellent protection against the ultraviolet rays between 2900 Å and 3100 Å that cause sunburn.

Harber[20] demonstrated the superiority of tannic acid and para-aminobenzoic acid as screening agents for ultraviolet light. However, tannic acid has been shown to be unstable on exposure to light.

Rothman stresses that para-aminobenzoic acid is preferable to its esters, which are used in many of the commercial preparations.[22] The esters are ab-

TREATMENT

In the treatment of solar dermatitis one first should attempt to determine, if possible, whether or not some photosensitizing agent is concerned. If this is true and the substance can be identified and eliminated, the reaction can be expected to disappear and not recur, as in most of Sams' cases, where lime oil and sunscreen agents were involved.[33, 34] Unfortunately, such is not the case usually, and no cause is evident.

First of all patients must be convinced of the need to avoid exposure to sunlight as completely as possible. Light out of doors, even on an overcast day, may contain a large amount of scattered ultraviolet "sky light." In those who are markedly sensitive even the light that reaches the skin in short exposures, such as a housewife may experience in emptying the garbage, shaking out a mop or hanging out a few clothes to dry, may be sufficient to prolong or to aggravate an eruption. Off-the-face hats, such as are in vogue at present, offer absolutely no protection. Yet it is difficult to convince a woman who is a victim of solar dermatitis that it is better to defy convention and wear a broad-brimmed hat or carry a parasol. Of course, there is a great deal of scattered and reflected light from sidewalks, white walls, water and so forth that cannot be avoided in this manner.

Protection of the extremities, the neck and the upper torso requires clothing with relatively high collars and long sleeves. Gloves also should be worn. Clothing that is too thin and porous may allow enough light to reach the skin to prolong or to flare a dermatitis.

Those whose occupation requires their being out of

doors are handicapped seriously by solar sensitivity. The most practical solution may be a change in work routine that enables them to work indoors. Occasionally night work can be substituted. Indoor work may be injurious to those sensitive to ultraviolet light if interior lighting with fluorescent lights is used, unless the ultraviolet part is screened out by an appropriate glass enclosure.[7]

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sorbed into the epidermis to a greater extent than the free acid; therefore, they are more common sensitizers. Rothman advised the use of Ruggle's vanishing cream as a base. Fisher [17] states that 15 per cent para-aminobenzoic acid in a base consisting of 20 per cent each of distilled water and hydrophilic ointment in a vanishing cream base makes an efficient and a *pleasant cream*

This type of cream is removed easily by washing This is a disadvantage in protection when exposure to sun is combined with swimming Kesten and Slatkin [22] find that carbolated petrolatum offers a marked degree of protection. This would not wash off so readily and, therefore, might be more satisfactory in *this situation One might be concerned regarding* toxic effects of absorption of phenol if large areas of the body were covered frequently with carbolated petrolatum Para-aminobenzoic acid in petrolatum would be desirable except for the difficulty of compounding a smooth preparation

Most of the commercial sunscreen preparations absorb only light below about 3000 A.[22] When light of longer wavelengths is involved, as in patients in whom porphyrins may be acting as photosensitizing agents, sunscreens having absorption spectra covering the longer wavelengths are needed One, proposed by Lerner and Lerner,[26] utilizes 50,000 units of beta carotene per Gm of water washable ointment base This has an absorption spectrum between 4000 A and 5000 A. Carotene also may be taken orally in doses of 50,000 units daily. Lerner and Lerner suggest that beta carotene might be combined with para amino benzoic acid and titanium dioxide to make a sun screen preparation with a wider range of efficiency

INTERNAL FACTORS

Because of the association of solar dermatitis and photosensitization by drugs, some of them used commonly, a careful drug history should be taken

The association of bacterial infections and solar sensitivity has been stressed[40] Search for and elimination of foci of infection should be considered Barber[1] recommended treating the large bowel as a source of bacterial toxins He advised enemas, laxatives and the administration of dilute hydrochloric acid and autogenous vaccines

Sonck[36] noted the frequent association of prurigo aestivalis and lymphogranuloma venereum

Impaired liver function has been associated by many, not only with abnormal porphyrin metabolism, but with light sensitivity in which no porphyria could be shown to be present Liver function studies, as well as tests for porphyrinuria, probably should be undertaken in all cases of idiopathic dermatoses caused by light Morgan, Shackelford and Lamb[28] believe that impaired liver function may result in important defects in the biologic transformation undergone by the steroid hormones in the body This may interfere with their normal physiologic effects and also with the inactivation of circulating estrogens They stress the effect of altered steroid hormone activity on the enzyme systems concerned in the metabolism of the skin, especially the character of the collagen tissues and the ground substance and the transformation of tyrosine to melanin. They used testosterone or gonadotropic hormone treatment with some success. The administration of estrogens also has been reported to be helpful[15, 23]

Stokes, Beerman and Ingraham[34] and many others have stressed the role of dietary deficiencies with regard to proteins, vitamins and minerals in the metabolic processes and health of the skin in relation to the development of solar dermatitis. The importance of thiamine, nicotinic acid, riboflavin and ascorbic acid has been stressed

Sodium para-aminobenzoate and antihistamines have been reported to be helpful when given orally.[41] Injections of gold salts and autohemotherapy have been advised.

More recently Atabrine, chloroquine and other synthetic antimalarials have been shown to be effective in improving or controlling many cases of light-sensitive dermatoses, as well as chronic discoid lupus erythematosus.[6, 23, 30] The mechanism of action of Atabrine and chloroquine is not yet understood If they act only as sunscreening agents, it would be illogical to expect them to help when the longer wavelengths of light are responsible, since for the most part they absorb light below 3500 A. Cornbleet suggests that the giving of more than one simultaneously may be advantageous, because their absorption spectra supplement one another[10] They should be avoided or used with caution when liver damage, leukopenia or other serious systemic diseases are present

Desensitization with gradually increasing doses of ultraviolet light has been helpful even in some cases of hypersensitivity to different wavelengths Probably this is helpful more often because of its effect in thickening the epidermis, particularly the stratum corneum, than because of hyposensitization in an allergic sense

SUMMARY

The procedures that on the average are most apt to apply are·

1 Attempt to discover and eliminate a possible photosensitizing agent (contact, drug or metabolite, such as porphyrin), determination of the action spectrum of the light responsible may help

2 Investigate regarding foci of infection, liver damage, endocrine disturbance or dietary or vitamin deficiency and institute appropriate treatment, if indicated

3 Educate as to the need for avoiding exposure and the ways and means of doing so.

4 Sunscreen agents topically—usually preparations containing para aminobenzoic acid.

5 Consider chloroquin or one of its relatives orally.

As is always the case, the variety of treatments recommended is due largely to the fact that none is successful regularly or outstandingly. Much remains to be learned

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4

Urticarial Hypersensitivity to Light*

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URTICARIAL HYPERSENSITIVITY to light plays its most important role in urticaria photogenica, but it is found also in other dermatoses associated with sun sensitivity, such as hydroa vacciniforme, eczema solare and prurigo aestivalis

SOLAR URTICARIA (URTICARIA PHOTOGENICA)

Solar urticaria, or urticaria photogenica, is a rare disease P Merklen (1904) reported two cases of urticaria due to sunlight and quoted older analogous observations by Joseph, Oppenheim, and Dinkelecker. The first detailed description of solar urticaria was given by Ward (1905), similar observations were reported later by Beinhauer, F Bernstein, Blum and West, Brunsting, Brugsch and O'Leary, Cummins, W Duke, Stephan Epstein,[9] Flandin and Laubry, W Frei, Goldschlag, Gougerot, Meyer and Peyre, Jausion and Pages, Ochs, Sellei, Urbach, Vallery-Radot and collaborators, Weiss, Wucherpfennig More recently Rajka, Prieto, Lopez de Azcona and Dochao, Blum,

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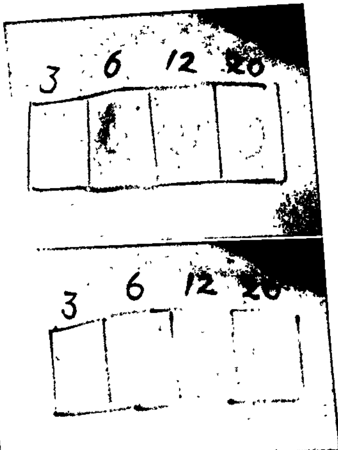


FIG. 1. Wheals caused by sunburn rays. Four fields were exposed to unfiltered mercury arc light (Kromayer lamp) for three, six, 12 and 20 seconds, respectively. (*Top*) Shows immediate whealing response that parallels the delayed sunburn reaction 24 hours later (*bottom*).

Barksdale and Green; Sulzberger and Baer,[21] Burckhardt;[7] Ehrlich; Beal; Epstein;[12] and Porter have reported informative studies of this condition. All in all, about 40 cases have been reported so far.

CLINICAL PICTURE

Urticaria photogenica consists of urticarial lesions at the site of exposure to the sun or other light sources (Fig 1). Lesions may occur on any part of the body, most often they are found on trunk, arms and legs because, as Blum and his co-workers have shown, the face and the hands may be up to 20 times less sensitive than the body, therefore, a dose of light that is enough to produce hives on the body may not be sufficient to evoke them on face and hands. With severe exposure to sunlight the patient may have general symptoms and malaise, he may even go into shock. Burckhardt[7] had such an observation. Ward noted the relationship between reaction and intensity of radiation (see Fig 1), with short exposure only erythema occurred, with longer irradiation, urticaria and even angioneurotic edema. In most instances a typical urticaria results, however, as in ordinary urticaria, especially due to drugs, combinations with other skin manifestations occur also in urticaria solaris. Duke noted that in cases with low sensitivity, prolonged exposure to the sun might produce a dermatitis.

In one of my patients moderate exposure to light was followed by urticaria, prolonged exposure by an acute dermatitis of the face. This case was especially interesting, because the patient presented on her arms clinically as well as histologically, the typical picture of prurigo aestivalis. Another patient of mine, suffering only from solar urticaria, responded with a

ONSET, COURSE AND PROGNOSIS OF URTICARIA SOLARIS

Solar urticaria usually begins suddenly. Urticaria photogenica may begin at any time of life, even in childhood. Not much is known about precipitating factors. In some instances overexposure to the sun marks the beginning of solar urticaria. In Porter's case it originated after an appendectomy, in several cases, similar to cold allergy, solar urticaria followed an insect bite or a sting from a ray fish, in other instances, it followed an infection.

In urticaria solaris females predominate, the ratio of females to males being about three to one. This prevalence is observed also in other light-sensitivity conditions, such as prurigo aestivalis (polymorphic light eruption) and hydroa vacciniforme.

With the exception of those cases caused by drugs, urticaria solaris lasts for many years and decades. I am not aware of complete cure in a single case of this type. However, in some instances there is a spontaneous improvement, especially in cases of sensitivity to ultraviolet light. Those patients who are sensitive to visible light only, apparently have a poorer prognosis and continue indefinitely without much change.

URTICARIAL HYPERSENSITIVITY TO LIGHT IN OTHER LIGHT SENSITIVITY DERMATOSES

Guenther, Ehrmann, Funfack, as well as Marten stein, reported urticarial reactions to light in their cases of hydroa vacciniforme. These reactions also have been found in cases of eczema solare and polymorphic light eruptions, even though the patients did not give a clinical history of solar urticaria. This latter observation is one of the reasons why Barber, Darier, Epstein,* Jausion, Rost and Keller believe that

delayed inflammatory reaction to exposure to longer ultraviolet (Fig. 2). These cases indicate a close relationship between urticaria solaris and eczema solare. It is likely that Veiel's case of eczema solare also belonged to the urticarial light dermatoses.



FIG. 2 Delayed inflammatory reaction to exposure to longer ultraviolet (Kromayer lamp through Corning filter 597, 22 minutes). Erythema, especially around follicles noted after two to six hours, gone after 24 hours; no pigmentation. No reaction in several normal controls.

spectrum but intermittent spectral lines Furthermore, they have an entirely different spectral distribution from the sunlight and have a relatively high rate of sunburn rays However, these lamps, especially the water cooled type—the so called Kromayer lamp—are very practical. This lamp can be put in contact with the skin to be tested, easily permits irradiation of small areas and often permits short exposures. A simple adapter makes exchange of light filters easy

The ideal way of determining the offending wavelengths is the use of monochromatic light, which is produced by a monochromator This apparatus permits the projection of the spectrum from the light source onto the skin Unfortunately, a monochromator is not easily available, and studies in solar urticaria have been carried out with such an instrument only by Beal,[3] by Burckhardt [7] and by Porter [18] In most instances the active wavelengths have been estimated by the use of colored filters, especially Corning filters, which allow certain wavelengths to pass through and absorb others These glass filters are very handy because they allow large quantities of light to pass through It is true that filters are not very exact, yet they do permit a definite distinction between solar urticaria attributable to ultraviolet rays and that form caused by visible light Even ordinary window glass can be used as a preliminary filter, because it does not permit ultraviolet rays below 3200 Angstrom units to pass through Whenever solar urticaria is produced through window glass, rays other than or in addition to the "sunburn spectrum" must be responsible Recently Porter described an "interference filter"

This is a filter in which the light is reflected between two partly silvered surfaces between which [illegible]

urticaria photogenica, eczema solare and prurigo aestivalis form one group of diseases, closely interrelated. The connecting link seems to be a photo-allergic mechanism.

EXPERIMENTAL STUDIES IN URTICARIA SOLARIS

Experimentally the lesions of solar urticaria are produced by the application of sunlight or light from other sources to a particular region of the body (see Fig. 1). The wheal is demarcated sharply, and covers about the area exposed, perhaps 1 or 2 mm. more. It is surrounded by an erythema that is not defined very clearly. Pseudopods never are observed in solar urticaria.

Spectral Ranges Responsible for Solar Urticaria. All parts of the visual spectrum, as well as the ultraviolet and the infrared, have been found to cause urticaria solaris. *The majority of patients with solar urticaria are sensitive to ultraviolet light, usually to radiation of less than 3700 Angstrom units, however, some are* sensitive only to radiation shorter than 3100 Angstrom units (Beal). Another clearly defined group of urticaria photogenica is that caused by blue and violet light between 4000 and 5000 Angstrom units. A third group is sensitive to the greater part of the visible spectrum, sometimes also to infrared, but usually not to ultraviolet.

Methods to Determine the Active Spectral Regions. The ideal source of light is natural sunlight. As this often is not available for experimental purposes, substitutes are used. Carbon arc lamp is the best, because this light also produces a continuous spectrum similar to the sun. The mercury vapor lamps are less well suited because they do not emit a continuous

spectrum but intermittent spectral lines Furthermore, they have an entirely different spectral distribution from the sunlight and have a relatively high rate of sunburn rays However, these lamps, especially the water cooled type—the so-called Kromayer lamp—are very practical This lamp can be put in contact with the skin to be tested, easily permits irradiation of small areas and often permits short exposures A simple adapter makes exchange of light filters easy.

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This is a filter in which the light is reflected between two partly silvered surfaces between which is interposed a sub-

stance such as zinc sulphide or any of the inorganic organic substances which are used in the blooming processes for increasing the transmission of lens systems

"In the lens blooming process a layer is deposited on the surface of the lens by a technique involving the evaporation of the substance in a near vacuum This layer is only a few thousandths of a millimeter thick but because of its optical nature it can increase or decrease the transmission of any specific wave-length of light, provided the thickness of the layer is correctly adjusted In the electromagnetic theory of light it is usual to refer to this layer material as *a dielectric* *The method of sandwiching the dielectric* between semimetallized surfaces merely exaggerates this effect. Therefore, as has been indicated above, for any given thickness of dielectric there is one preferential wavelength transmitted, and by making a nonuniform deposit in the form of a wedge it is possible to obtain a continuous succession of transmission bands "

PHOTO ALLERGY

Only lately has the concept of photo allergy as an *important mechanism in photosensitivity diseases been* accepted generally, probably because for a long time it was supported only by circumstantial evidence However, the photo-allergic phenomenon now has been proved experimentally in the case of photosensitivity from sulfanilamide (Epstein [10] and Burckhardt [8]) Sulfanilamide shows a weak photodynamic action that can be demonstrated in every person when a sufficient quantity of sulfanilamide is injected and irradiated with *enough ultraviolet rays to produce a strong ery*thema. This photodynamic, or phototoxic, reaction occurs within 24 hours. However, several tested persons became photo-allergically sensitive to sulfanilamide. The photo allergic reaction which occurred about the ninth day after the sensitizing experiment, showed characteristics different from the phototoxic

reaction and could be elicited later on by injecting weak solutions of sulfanilamide and using suberythema doses of ultraviolet light That this photo-allergic mechanism is responsible for photodermatitis [illegible]

[illegible] following sulfanilamide therapy, as first reported by Brunsting, is based on a photo-allergic mechanism, though this has not been proved in his and other (Epstein [19]) cases A photo-allergic mechanism also has been proved by Sams [20] in photo contact dermatitis from Persian lime, as well as from certain sun protective creams

ALLERGIC NATURE OF URTICARIA SOLARIS

The allergic nature of solar urticaria has been suspected for a long time (Duke, A. Rowe, Sellei, F Bernstein, and others) The main reason for such an assumption in regard to urticaria solaris, eczema solare and prurigo aestivalis probably was their clinical resemblance to ordinary urticaria, eczema and prurigo. It is true that wheals can be produced by other than allergic mechanisms Photodynamic substances, such as hematoporphyrin and eosin, will produce whealing when irradiated after intracutaneous injection Although at times these wheals seem to be indistinguishable from those occurring in urticaria photogenica, actually they are different With strong irradiation the photodynamic wheal turns into a hard infiltrated lesion followed by pigmentation, something that does not occur with the wheals of solar urticaria Furthermore, as Blum has shown, molecular oxygen is necessary for the photodynamic reaction but not for the lesions of urticaria solaris But what is the allergen in this condition?

stance such as zinc sulphide or any of the inorganic organic substances which are used in the blooming processes for increasing the transmission of lens systems.

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for one hour at 60° C. abolished its capacity to transfer the light hypersensitivity to normal skins

2. One full reaction-producing exposure of a site sensitized passively sufficed as a rule to exhaust its capacity to react, similar to the phenomenon seen in sites sensitized passively with the Prausnitz-Kustner reagins

3. There were no known photodynamic, photosensitizing chemicals (porphyrins, etc) demonstrable in the patient's serum

4 If not exposed to light the sites of serum depot do not diminish in sensitivity to light but give maximum reactions four days or more after their injection into the normal skin (whereas photodynamic reactions have their maximum three to six hours after injection)

Sulzberger and Baer interpret the fact that passive transfer reactions apparently can be elicited in everybody and at any time by the suggestion that the antigen with which the antibody reacts is a *substance that* normally is produced in the *skin of all human beings on exposure* to sunlight or to ultraviolet irradiation Although subsequent experimenters have found that passive transfer with the serum of the same patient cannot be elicited always in all persons at all *times*, this does not invalidate Sulzberger and Baer's theory, because it can be explained easily by the amount of antibody present in the donor's serum As Rajka,[19] and later Beal,[3] as well as Epstein,[12] have shown, the antibody of the donor's serum is increased when he is irradiated before the serum is taken However, Rajka believed that the existence of a secondary allergen, i e, one produced in every skin on physical irritation, was disproved by the failure of the passive

About 50 years ago, Joseph Jadassohn, discussing dermatoses caused by physical agents, suggested that these physical forces produced substances in the skin that had a damaging effect upon it Sellei (1930) declared that physical allergies differed from those caused by chemical agents only in that the role of the antigen was played not by a well-defined chemical but by a substance that was produced within the organism by the physical agent Bernstein (1933) voiced a similar opinion. Epstein (1939) suggested that we were dealing with an allergy against a body own substance that was produced normally by irradiation Sulzberger and Baer, in regard to solar urticaria, have elaborated convincingly on this theory, i e., that the allergen in this disorder was a normal metabolite of the skin produced by the sun's rays This theory, which applies to solar urticaria caused by rays of a wavelength of less than 3700 Angstrom units, now is accepted generally

The main proof of the allergic nature is the passive transfer test, which frequently is positive in urticaria photogenica due to ultraviolet A positive passive transfer by itself is not absolute proof of an allergic mechanism, because a photosensitizer may be transferred instead of an antibody Therefore, Muhlman and Akobjan considered the successful passive transfer as indication of a photodynamic reaction, whereas Bernstein interpreted it as an allergic phenomenon. Sulzberger and Baer [21] support the viewpoint that the passive transfer of the urticarial sensitivity in their case was due to the presence of an antibody (reagin) in the blood stream by the following facts

1. Similar to the thermolabile antibody of the Prausnitz Küstner reaction, incubation of the serum

for one hour at 60° C. abolished its capacity to trans fer the light hypersensitivity to normal skins

2 One full reaction-producing exposure of a site sensitized passively sufficed as a rule to exhaust its capacity to react, similar to the phenomenon seen in sites sensitized passively with the Prausnitz-Kustner reagins.

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transfer test in reverse, because, as he states, irradiation followed by the injection of serum containing reagin is not successful. However, more recent studies by Epstein [12] have shown that the passive transfer in reverse in solar urticaria is positive.

In this test the serum of the light-sensitive patient is injected into the skin of the recipient within five to 30 minutes after irradiation. In some of these tests immediate whealing reactions occurred; in others, no clinical reaction was noted However, when these sites were irradiated 24 hours later, they failed to produce a reaction, thus indicating that the antibody had been exhausted previously by a subclinical reaction The positive passive transfer in reverse in urticaria photogenica clinches the argument for the allergic nature, because this phenomenon can be explained only on an antigen-antibody basis, and not by the assumption of a photodynamic action. A photodynamic substance will not produce a reaction when injected into skin irradiated previously, because it needs the energy of the photon to be activated.

The theory that the antigen in solar urticaria is a normal metabolite of the skin apparently does not help us in those cases that are sensitive only to visible light; for instance, the blue and the violet rays Visible light is not known to have any metabolic effect on the skin besides the heat effect It would seem most likely that in these instances an abnormal sensitizer is present in the skin. As these patients react to different spectral regions, it is likely that more than one sensitizer is responsible Nothing definite is known about the nature of these sensitizers So far there is no evidence that porphyrins are the sensitizers, although their role as allergens has not been ruled

out The presence of an abnormal antigen not present in normal skin would explain readily why the passive transfer in urticaria solaris due to visible light only is usually negative However, Kesten [14] reported a positive passive transfer in a patient with sensitivity to blue and violet light. One may explain such an occurrence by the assumption that the serum of the patient contained both the antibody and an antigen (photosensitizer) or, more correctly speaking, the proantigen, i e, that substance which becomes a real antigen by irradiation Antibody and proantigen can coexist peacefully in the same serum, because a reaction takes place only after the proantigen has been activated into the real antigen That such a mechanism exists has been made probable by studies in prurigo aestivalis (Epstein [11]) The photo allergic concept of prurigo aestivalis has been presented as follows

A union of antigen and antibody must occur in order to provoke a reaction In the skin of the photoallergic person the antigen is created by the influence of irradiation on a precursor substance, or proantigen, which is present This antigen may be fixed or circulating, a body own substance or an extraneous one By themselves, neither proantigen nor antigen is capable of provoking a visible reaction, thus

Proantigen + Light = Antigen (no visible reaction)

Certain individuals possess the capacity to produce antibodies to such an antigen during the course of a suitable incubation period These antibodies may be fixed or circulating By themselves the antibodies can provoke no visible reaction Neither can they combine with proantigen to produce such an effect, thus

Proantigen + Antibodies = No reaction.

In the sensitized individual, the union of antibodies and antigen (the converted proantigen) provokes a visible effect in the form of a wheal or an inflammatory reaction, thus.

Proantigen + Light + Antibodies = Visible reaction.

Under certain conditions when the skin is sensitized the irradiation of a circumscribed area may provoke a visible reaction, not only at the local site, but also at a region remote from the point of exposure. This effect results from the union of circulating antigen, released from the irradiated site, with fixed antibodies at the remote site.

There are a few cases of solar urticaria in which the essential sensitizer is known, i.e., those following treatment with sulfanilamide (Brunsting, Epstein). In these instances the sensitivity to light lasted only several weeks. "*Spontaneous desensitization within a few weeks*" in a case of sunlight urticaria was reported by F. Bernstein.[4] His patient, suffering from alopecia areata, had been treated with ultraviolet simultaneously with chemicals, such as phenol and mercurials. Because of the short duration of the sensitivity, I would assume that in this case also there was a photoallergic mechanism based on drug sensitivity. Passive transfer from man to man was negative in Bernstein's case. The results of his transfer tests on animals suggest a phototoxic rather than an allergic phenomenon.

TREATMENT

Treatment of solar urticaria usually is not too satisfactory, especially in those cases caused by visible light. In patients sensitive to ultraviolet light, the antihista-

mines are more or less helpful. The first successful report is by Tyson.[27] He achieved prompt relief in a case of solar urticaria treated with Benadryl. The sunburn protective action of antihistamines has been studied by Kurtin, Bierman and Yontef,[17] by Borelli,[5] by Baer, Kline and Rubin,[2] by Kline and Baer,[16] and by Friedlaender, Friedlaender and Vandenbelt.[12] However, their investigations indicated that this effect was not due to the "antihistaminic" action but to the physical properties of Pyribenzamine. This drug absorbs the active wavelengths causing sunburn and, therefore, prevents them from reaching the skin. The absorption curve of Pyribenzamine shows a high extinction peak in the zones producing ultraviolet erythema. Baer, Kline and Rubin corroborated their theory by additional experiments. They were able to protect the skin from sunburn reaction by placing the Pyribenzamine solution in quartz cups between the skin and the source of light, thus excluding any chemical effect on the skin. Furthermore, Benadryl, which shows no absorption within the sunburn spectrum, evidenced only a slight diminution of the ultraviolet erythema. However, these experiments do not exclude the possibility that there also may be some other mechanism by which the "antihistamines" act as protection against ultraviolet. Borelli studied the effect of oral medication of the antihistaminic drug Dimentina (dimethyl aminoethylbenzylamline) upon the ultraviolet reaction of the skin. In the majority of cases a rise of the threshold erythema was noted, also an increase of the latent period and a diminution of the degree and the duration of the erythema. The pigmentation was less severe only occasionally. However, the subjective symptoms such as burning and

itching were missing, even if they had been present and still existed in areas that were irradiated as a control on the preceding day. Borelli concludes from his studies that a great part of the so-called antihistaminic (anti-allergic) actions of these drugs is due to *their anesthetic capacity*.

Desensitization to sunlight with gradual exposure has been recommended and helpful in some instances By combining oral Pyribenzamine with increasing doses of ultraviolet Beal[8] was able to increase greatly the patient's tolerance to light in the treated areas, however, nontreated areas did not show any greater resistance, indicating that the latter had been produced by physical means and not by allergic desensitization. Many nonspecific measures have been tried with more or less success in sun-sensitivity diseases in general, such as eradication of focal infections, treatment with female or male hormones and antimalarial drugs The *latter treatment, often helpful in prurigo* aestivalis, "appeared to be of value" in Porter's[19] case, he gave chloroquine sulfate, 150 mg. twice daily According to Baer,[1] a number of patients with solar urticaria have done much better on treatment with antimalarial drugs.

Protection against light by avoiding exposure and wearing protective clothing still is the most important therapeutic measure Those cases caused solely by sunburn rays *should have protection from substances* that absorb the sunburn spectrum As Rothman has shown, para-aminobenzoic acid (PABA) is an ideal protective agent against sunburn rays, however, para-aminobenzoic acid does not filter out the long ultraviolet, which also is involved in solar urticaria Beal's patients were not protected by PABA; neither

were mine. However, chemicals that act as physical barriers against light, such as titanium dioxide or zinc oxide provide some protection also against the longer ultraviolet rays and visible light.

SUMMARY

Urticarial sensitivity to light is discussed in regard to its clinical aspects and causation. The allergic nature of urticaria solaris appears to be well proved, but so far nothing definite is known about the antigens and only little about the mechanism involved.

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itching were missing, even if they had been present and still existed in areas that were irradiated as a control on the preceding day. Borelli concludes from his studies that a great part of the so called antihistaminic (anti-allergic) actions of these drugs is due to their anesthetic capacity.

Desensitization to sunlight with gradual exposure has been recommended and helpful in some instances By *combining oral Pyribenzamine with increasing* doses of ultraviolet Beal[3] was able to increase greatly the patient's tolerance to light in the treated areas; however, nontreated areas did not show any greater resistance, indicating that the latter had been produced by physical means and not by allergic desensitization. Many nonspecific measures have been tried with more or less success in sun sensitivity diseases in general, such as eradication of focal infections, treatment with female or male hormones and antimalarial drugs. The latter treatment, often helpful in prurigo aestivalis, "appeared to be of value" in Porter's[18] case. he gave chloroquine sulfate, 150 mg twice daily According to Baer,[1] a number of patients with solar urticaria have done much better on treatment with antimalarial drugs

Protection against light by avoiding exposure and wearing protective clothing still is the most important therapeutic measure Those cases caused solely by sunburn rays should have protection from substances that absorb the sunburn spectrum As Rothman has shown, para aminobenzoic acid (PABA) is an ideal protective agent against sunburn rays, however, para-aminobenzoic acid does not filter out the long ultraviolet, which also is involved in solar urticaria Beal's patients were not protected by PABA, neither

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Hypersensitivity to Heat

OTIS F. JILLSON, M.D.
Hanover, New Hampshire

INTRODUCTION

THERE ARE TWO FORMS of hypersensitivity to heat [1] (a) generalized (cholinogenic) urticaria produced by heat, exercise and emotional stress, and (b) local (noncholinogenic) urticaria produced by heat alone, and usually only on the area of skin exposed to heat. This localized form is rare and of little clinical importance However, the generalized form, referred to by Hopkins and Kesten [2] as cholinogenic urticaria, has opened the way to the elucidation of a number of dermatologic problems For example, it is one skin disease where the mechanism is known by which a psychic stimulus can produce a definite lesion in the skin It appears to be conceivable also that a cholinogenic mechanism may play an important role in the production of itching in atopic dermatitis.

GENERALIZED (CHOLINOGENIC) URTICARIA PRODUCED BY HEAT, EXERCISE AND EMOTIONAL STRESS

Clinical Picture The urticaria is produced by heat of a warm room, hot foods, a hot day, clothes, fever

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cholinogenic urticaria can curtail many activities and even incapacitate some patients.

Mechanism. The mechanism for the production of cholinogenic urticaria is well known and is based on the following observations by Grant and his group [3]

1. If one leg of a patient with cholinogenic urticaria is placed in water heated to 100° F for from 20 to 30 minutes, a generalized urticaria will appear. It is necessary to raise the body temperature 0.2° to 1° F to produce a reaction.

2. If before such a test the venous circulation of the leg is occluded by a cuff, no wheals appear anywhere on the body until after the cuff is released and circulation is restored. This indicates that the essential stimulus is transmitted from the heated skin by the blood stream and not by the nervous system. The heated blood is carried to the brain to act on some central heat regulating mechanism. This in turn stimulates the nervous system to carry impulses to the skin, where the chemical in question is released to produce the characteristic skin lesions.

3. If in a similar experiment the arterial circulation to one arm is occluded by a cuff, bluish lesions can be noted on the occluded arm. When the circulation is restored, wheals appear in these bluish areas. This indicates that the stimulus is carried to the area in which wheals develop by nervous impulses from the brain and not by the blood stream.

Pharmacologic Studies. Subcutaneous injection of from 0.2 to 0.5 mg. of carbachol (Doryl) or 12 mg. of methacholine (Mecholyl) will produce a generalized reaction of cholinogenic urticaria, whereas both iontophoresis and intradermal skin testing can be utilized to demonstrate hypersensitivity to heat locally

or a hot bath. Emotional stress, where the patients get all "het up," and exercise can produce identical reactions. In some cases a combination of these three factors, such as may occur in dancing or various sports, may be necessary to bring out an episode of this urticaria.

The lesions themselves are so characteristic that the disease can be diagnosed clinically. They are small 1 to 2 mm. wheals, surrounded by a large axone reflex flare. When the lesions are confluent, huge patches of erythema are noted. Bright red flares are sometimes the only visible lesions, the beadlike central wheals appearing only occasionally. This type of distinctive urticaria can appear anywhere on the body, except that skin lesions or itching never occur on the palms and the soles, and rarely in the axillae. There is a second type of lesion that is characterized by minute discrete 1 to 3 mm. wheals. These are found especially on the extremities.

Nomland[8] described as cholinogenic itching the intense pruritus without urticaria that developed in some patients when they were exposed to heat, exertion or emotional stress. Angioneurotic edema has been described as being present in many of these patients,[3] and more recently it has been claimed that in exceptional cases erythema nodosum and purpura perhaps also can be based on a cholinogenic mechanism.[9]

In about 50 per cent of these patients, where there is a sufficient release of acetylcholine, systemic manifestations such as abdominal cramps, diarrhea, faintness, sweating, salivation and headaches occur.

Usually there are repeated transient episodes of this disease complex, the total duration being from several months to ten to 15 years. When severe,

Pilocarpine, which acts directly on nerves innervated by postganglionic cholinergic fibers, also produces urticaria in these patients These pharmacologic studies demonstrate that it is acetylcholine that is responsible primarily for the sensitivity reaction in this type of urticaria

Morgan[7] suggested, but was unable to prove, that there might be a deficiency in the enzyme cholinesterase, thereby permitting a prolongation of the normal action of acetylcholine or its persistence in undue quantities

To recapitulate, the mechanism for the production of hypersensitivity to heat can be explained as shown in Figure 3 When exercise, heat and emotions, or a combination among the three, increase the body temperature from 0 2° to 1° F , they cause the warmed blood to stimulate some heat-regulating center in the brain This in turn sends nerve impulses along cholinergic nerves of the parasympathetic nervous system, which then releases its chemical mediator, acetylcholine The skin of subjects who presumably are hypersensitive to this chemical then reacts with the production of cholinogenic urticaria A peripheral nerve block with procaine, which interrupts the centrifugal nerve impulses, will prevent them from reaching the skin and thus also the development of urticaria in its area of distribution

It is assumed that these patients are allergic to acetylcholine, but passive transfer tests have been negative Therefore, some investigators[9] have suggested a final release of histamine, but this appears to be highly unlikely, since certainly in cholinogenic itching, where there are no urticarial lesions, histamine release is not a factor Also, there is no increase

By iontophoresis, acetylcholine bromide 0.2 per cent (with 0.01 per cent eserine sulfate added) is introduced into the skin at the positive electrode. A current of 2 milliamperes is applied for two minutes.[7] If results are equivocal in comparison with controls, it is recommended that a current of 0.5 milliampere (20 microamperes per sq. cm.) be allowed to flow for 20 minutes. The diagnostic reaction is the appearance in one to five minutes after iontophoresis of numerous small white wheals in the area where the electrode was applied.[3]

For intradermal testing, Mecholyl 0.01 mg. dissolved in 0.05 cc. physiologic saline is used. In normal persons a 7 to 8 mm. wheal surrounded by a *narrow flare (maximum diameter 15 mm.) appears* after a few minutes. In susceptible persons the wheal is of about the same size, but the flare is much larger and contains the characteristic minute wheals of cholinogenic urticaria.[3]

Acetylcholine introduced into the skin by subcutaneous injection or iontophoresis produces urticaria irregularly in patients with cholinogenic urticaria. It is unstable, being destroyed rapidly by the enzyme cholinesterase. If acetylcholine is introduced into the skin simultaneously with physostigmine, urticaria is produced regularly in about ten minutes. Physostigmine exerts its pharmacologic activity in the body by inhibiting cholinesterase in body fluids and tissues, thus preventing the inactivation of acetylcholine. The longer-acting cholinergic drugs, such as methacholine (Mecholyl) and carbachol (Doryl), consistently will produce urticaria. These drugs are hydrolyzed less readily by cholinesterase than is acetylcholine, and this is the basis for their longer duration of action.

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of typical relatively large wheals as seen in urticaria due to cold, light and other causes The lesions do not spread beyond the area of contact. No systemic symptoms have been reported. If they occurred, they would be expected to be of the type seen in urticaria due to cold and light The disease cannot be reproduced by injection or iontophoresis of cholinergic drugs, but is said to have been induced in a generalized form by systemic administration of fever-producing drugs Passive transfer tests have been unsuccessful[3, 4]

The simplest method of testing consists of immersing one hand and forearm in water at 100° F (about 38° C.) for five minutes Flushing is noted upon withdrawal of the exposed area This is followed in five minutes by a uniform tense wheal[4]

TREATMENT

In the cholinogenic generalized type of heat urticaria the mechanism of the disease has been elucidated and agreed upon by various investigators It would be logical to assume that treatment directed in a scientific manner against the etiologic factor, acetylcholine would be effective, but anticholinergic therapy is strikingly disappointing

Various anticholinergic drugs such as the tertiary amines atropine or Syntropan are without consistent effectiveness Likewise, the newer quaternary amines such as the Banthines and Prantal are of little value in the treatment of cholinogenic urticaria. This can be explained by the fact that these drugs act directly on the effector cells and not on the nerve endings In other words, the anticholinergic substances do not prevent the release of the chemical mediator acetyl-

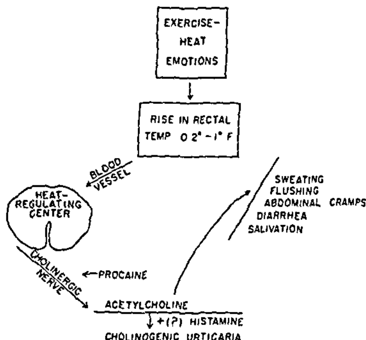


Fig 3 Mechanism of hypersensitivity to heat.

in gastric acidity following an acute episode of cholinogenic urticaria

LOCAL (NONCHOLINOGENIC) URTICARIA PRODUCED BY HEAT

The rare local type of urticaria produced by heat differs markedly in clinical appearance and in its basic mechanism from the generalized cholinogenic type. The lesions are produced only on areas of skin exposed to heat by contact and not by physical exertion or psychic stimuli Clinically the eruption consists

of typical relatively large wheals as seen in urticaria due to cold, light and other causes. The lesions do not spread beyond the area of contact. No systemic symptoms have been reported. If they occurred, they would be expected to be of the type seen in urticaria due to cold and light. The disease cannot be reproduced by injection or iontophoresis of cholinergic drugs, but is said to have been induced in a generalized form by systemic administration of fever-producing drugs. Passive transfer tests have been unsuccessful.[1,2]

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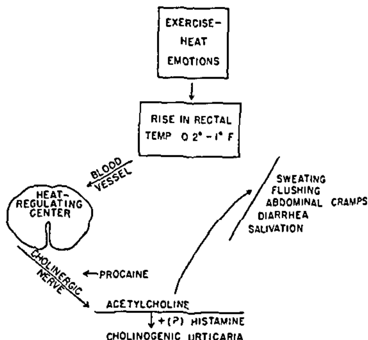


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choline. I suppose that the failure in treatment bespeaks the allergic etiology of the disease; i.e., there is not an abnormal quantitative release of acetylcholine in these patients. Their hypersensitivity is to minute "amounts" of this chemical released normally, which is in keeping with allergic principles.

Antihistamines do give partial but not dependable relief of symptoms This does not favor necessarily the theory of a final release of histamine. These drugs have many pharmacologic actions other than antihistaminic. They may have an atropinelike action on smooth muscles and glands, or they may inhibit the action of hyaluronidase.[8]

Of great practical importance is the fact that there is a period of freedom after an attack of cholinogenic urticaria—a refractory period or an unresponsive period After a moderate episode of urticaria, this unresponsiveness may last for hours, but after a generalized severe episode, produced either by warming the leg for an hour or by injecting subcutaneously 0.5 mg. of Doryl, this period of freedom may persist for a day or two This is of therapeutic value and can be utilized before one goes to a dance or a sporting event.

To quote Kierland [4]

> Attempts at desensitization by means of immersion of one part of the body, such as a hand or forearm, in water of gradually increasing temperature occasionally may produce satisfactory results First the temperature of the water is below the threshold at which symptoms are produced, usually at body temperature, and then the temperature of the water is increased gradually up to that which produces symptoms. The temperature is then decreased and very gradually increased again, in the hope that the threshold level can be passed and that the patient ultimately will be

desensitized to the effects of heat. The same type of treatment is applicable to those who have the local contact type of hypersensitivity to heat.

Another very practical therapeutic measure that is effective in abating an attack is the application of cold or iced water to the hands and the arms. This, plus rest, consistently will abort or prevent cholinogenic urticaria and is the treatment of choice for this disease. In addition, each patient can attempt to determine what the threshold of exercise, heat and the various emotions is that produces the urticaria and attempt limitations of his activities accordingly.

In the noncholinogenic type of heat urticaria the same therapeutic measures as in the cholinogenic form are likely to be effective.

CONCLUSION

Urticaria due to heat can be divided into the generalized type (cholinogenic urticaria) produced by heat, exercise and emotional stress and a noncholinogenic "local" type produced by heat alone.

Cholinogenic urticaria is a disease in which the basic physiologic chemical mechanism is understood so fully that one would expect that therapy directed against the responsible agent, acetylcholine, would be effective. However, anticholinergic drugs are ineffectual.

The most effective treatment for both forms of heat urticaria follows simple logic. In these patients the reactions are produced by heat, therefore, the treatment of choice is to rest and to cool the body. Antihistamines and "hyposensitization" to heat, as well as other measures, also have proved to be beneficial in some cases.

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6

Cutaneous Sensitivity to Cold

Sylvia F. Griem, M.D., Stephen Rothman, M.D.

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ALTHOUGH REPORTED as early as 1866 by Bourdon and Behier and described in detail by Blachez in 1872,[illegible] urticaria due to cold did not arouse great medical attention until 1924, when Duke[illegible] published a case of cold urticaria and propounded the concept of physical allergy. Since then hundreds of cases have been reported, and numerous investigators have studied the mechanism of cold sensitivity. However, few questions have been answered. Is cold sensitivity a true allergy based on an antigen-antibody mechanism? If so, how does cold act as an antigen? Are the mechanisms of idiopathic cold urticaria and the cold urticaria associated with cryoglobulinemia and syphilitic paroxysmal cold hemoglobinuria similar? These problems and many more deserve further investigation.

On the basis of clinical and serologic studies the following types of cutaneous sensitivity to cold can be distinguished:

1. Cryoglobulinemia.
2. Syphilitic paroxysmal cold hemoglobinuria.

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Lerner, Barnum and Watson[40] studied sera from 121 patients suffering from a variety of diseases (empyema, bronchiectasis, brucellosis, rheumatic heart disease, etc.) and noted cryoglobulins in 31. No cryoglobulin was found in 40 normal sera. Only one of these sera showed a level above 25 mg. per cent. They considered a level above 25 mg. per cent to be significant. Although one case of severe cold sensitivity with a cryoglobulin of 22 mg. per cent has been reported,[4] symptoms attributable to cryoglobulins usually do not occur below 500 mg. per cent.

Cold sensitivity has been reported in two-thirds of the cases of cryoglobulinemia other than those associated with kala-azar and subacute bacterial endocarditis.[33] Purpura on exposed surfaces is the most common manifestation, but cold urticaria, Raynaud's phenomenon, necrosis, ulceration and conjunctival, oral, nasal and retinal hemorrhages have been reported frequently. It is quite common for an individual to develop cold urticaria first and purpuric and other lesions months to years later.

The cutaneous findings are associated with capillary thromboses on the surfaces exposed to cold, but the exact mechanism of their production is not established. Rorvik[35] suggests the following possibilities: (1) increase in blood viscosity, (2) precipitation of cryoglobulins in peripheral vessels, (3) intravascular agglutination of erythrocytes, (4) amyloid degeneration in the vascular walls with abnormal fragility (in myelomatosis only), and (5) fibrinogenopenia.

The urticarial wheal produced by cold exposure in cryoglobulinemia shows the typical histaminic triple response, as do the wheals of other types of cold urticaria. Whether the urticaria in cryoglobulinemia is

3. Cold hemagglutination.
4. Essential cold urticaria †

CRYOGLOBULINEMIA

The first published occurrence of cold-precipitable proteins in serum was a case with associated purpura reported by Wintrobe and Buell in 1933.[73] Only eight additional cases were reported up to 1947, when Lerner and Watson[42] published their studies and coined the term *cryoglobulinemia* to describe the abnormal globulins that precipitate from the serum on cooling and redissolve on warming. Cryoglobulins have been the subject of intensive research in the past decade, and many new cases have been reported.

A simple screening test for cryoglobulins is performed by drawing venous blood into a syringe that has been warmed to 37° C. and allowing it to clot at 37° C. The serum is separated and is cooled to 5° C. Cryoglobulins precipitate as small discrete white particles that dissolve when the serum is rewarmed to 37° C. The cryoglobulins may precipitate at room temperature if they occur in high concentrations.

Cryoglobulins are present in large quantities in kala-azar[73] and in very small amounts in subacute bacterial endocarditis.[10] Although rare in multiple myeloma, one-half of the reported cases of cryoglobulinemia have occurred in this disease.[13] Chronic lymphatic leukemia has been reported in one-fifth of the cases[13] and rheumatoid arthritis[27] and "liver disease"[5] in isolated cases. We have observed a case of Weber-Christian disease with cryoglobulinemia.[31]

† It has been claimed also that a specific "cold eczema" exists. However, the literature on this entity is scant and not quite convincing.[8, 21, 63, 67]

erner, Barnum and Watson[40] studied sera from 121 patients suffering from a variety of diseases (empyema, bronchiectasis, brucellosis, rheumatic heart disease, etc.) and noted cryoglobulins in 31. No cryoglobulin was found in 40 normal sera. Only one of these sera showed a level above 25 mg per cent. They considered a level above 25 mg. per cent to be significant. Although one case of severe cold sensitivity with a cryoglobulin of 22 mg. per cent has been reported,[4] symptoms attributable to cryoglobulins usually do not occur below 500 mg per cent.

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The urticarial wheal produced by cold exposure in cryoglobulinemia shows the typical histaminic triple response, as do the wheals of other types of cold urticaria. Whether the urticaria in cryoglobulinemia is

based on an antigen-antibody reaction or whether it is produced by histamine liberated by the tissue damage produced by cold, or whether or not the cryoglobulin is directly responsible, is unknown. Steinhardt and Fisher[85] were unable to obtain a positive passive transfer test with the serum of their patient with cold urticaria and essential cryoglobulinemia However, a positive passive transfer was obtained with the cold-precipitable portion of the serum. The phenomenon of exhaustion of antibodies was suggested by the refractoriness of exposed sites in the patient to further cold stimulation ACTH and cortisone did not change the intensity, the duration or the size of the wheal formation. However, Benadryl reduced the whealing response in their case. Antihistamines also were effective in Pelzig's case[48]

Electrophoretic curves of serum in essential cryoglobulinemia show a rise in globulins, especially the gamma fraction[86] In an analysis of cryoglobulins from a patient with acropurpura, chronic glomerulonephritis and congestive heart failure, Lerner and Greenberg[41] found that, except for difference in solubilities, molecular weight and viscosity, the globulin resembled closely gamma globulin. More recently, Putnam[51] in basic studies dealt with cryoglobulins and other abnormal globulins and found that patients with multiple myeloma had a perverted mechanism of protein synthesis. They may make abnormal globulins, including cryoglobulins, that individually are specific, as shown by immunologic and chemical analysis Apparently the body has lost its ability to produce the diverse spectrum of normal globulins.

A search for cryoglobulins should be made in all patients manifesting without obvious cause cold urti

caria, Raynaud's phenomenon, purpura, multiple myeloma and hemorrhages from mucous membranes

SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA

Although the incidence of cold urticaria in syphilitics with paroxysmal cold hemoglobinuria is not known accurately, it is great enough to consider its association as more than coincidental, particularly as the syndrome disappears if antiluetic therapy is administered

In the early 1900's Donath and Landsteiner demonstrated in the sera of syphilitics with paroxysmal cold hemoglobinuria the presence of a cold hemolysin that united with erythrocytes in the cold and, upon rewarming in the presence of complement, caused hemolysis Estimates of the incidence of cold hemolysins range from one in 360 patients in all stages of syphilis to 20 per cent of persons with late latent syphilis It is even more common in late prenatal syphilis. No cold hemolysins have been reported in secondary syphilis Usually they are limited to those subjects who do not show other clinical evidence of active syphilis.

Syphilitic paroxysmal cold hemoglobinuria occurs when an individual with cold hemolysins is rewarmed after exposure to cold Hemolysis of red blood cells occurs with release of hemoglobin into the circulation, and if the hemoglobinemia exceeds the renal threshold, hemoglobinuria results If hemolysis is severe, shaking chills, fever, sweats, abdominal cramps, weakness headache, backache and vomiting may precede the passage of red urine

Cold urticaria may be one of the presenting symptoms or it may be latent, as in the case of Davis and Rosenbaum, in which an urticarial wheal was pro-

duced by application of ice to the skin but cold urticaria did not appear clinically. Raynaud's phenomenon also has been reported in association with syphilitic paroxysmal cold hemoglobinuria.[16, 45]

In a series of careful experiments on sera of patients with syphilitic paroxysmal cold hemoglobinuria associated with cold urticaria, Harris, Lewis and Vaughan[21] were able to transfer the skin-sensitizing factor of the serum to the normal skin of other syphilitic subjects and elicit an urticarial response by application of cold to the site of transfer. They coined the term *dermolysin* for this skin-sensitizing factor of the serum and suggested that it was similar to, if not identical with, the cold hemolysin. Both hemolysin and dermolysin were removed from the serum by adsorption with the patient's own erythrocytes in the cold. In one case, after adsorption on sheep red blood corpuscles the serum lost its hemolyzing ability but remained active in the passive transfer test for cold sensitivity. However, no further studies were done to determine whether or not dermolysin and hemolysin actually were separate entities

Becker[6] found that antihistamines controlled the cold urticaria in his patient, although they had no effect on the cold hemoglobinuria. Antiluetic treatment benefited all symptoms. However, the Wassermann reagin and cold hemolysin titers remained strongly positive.

By differential adsorption of the factors in the cold, Mackenzie[45] has well established that Wassermann reagin and cold hemolysin are separate entities. More recently Jordan[31] has shown the separate identity of the Donath Landsteiner hemolysin and the TPI antibody.

COLD HEMAGGLUTINATION

Cold hemagglutination is a serologic reaction in which there is agglutination of homologous or heterologous erythrocytes at low temperatures with complete reversal of the reaction upon rewarming. No complement is required for this reaction, and hemolysis does *not* occur *in vitro* unless the system is shaken or otherwise traumatized.

Cold hemagglutinins were discovered in animals by Landsteiner in 1903,[55] they were found to occur also in man in 1918.[56]

A low titer of these agglutinins is found in 95 per cent of normal healthy persons.[57] Higher titers occur in a variety of pathologic states such as primary atypical pneumonia, trypanosomiasis, tropical eosinophilia, infectious mononucleosis, hemolytic anemia, rarely in leukemia and lymphoblastomas, and idiopathically. The cold agglutinins of normal and pathologic sera are identical and differ only in titer. By electrophoresis they have been determined to be globulins.

The titers of cold hemagglutinins in patients with symptoms attributable to this antibody vary widely, levels of 1:80 to 1:168,000,000[57] having been reported. The agglutinin titer is not related directly to the type or the degree of symptoms, but the thermal range doubtless is important, especially in low titer sera.

The cutaneous manifestations of this type of sensitivity to cold are primarily of an ischemic nature due to obstruction of the circulation by agglutinated erythrocytes following exposure to cold. Gangrene, ulcers, Raynaud's phenomenon and acrocyanosis frequently have been reported. The classic cold *urticaria* has

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Intravascular hemolysis resulting in anemia and paroxysmal cold hemoglobinuria occurs probably as a result of trauma to the agglutinated erythrocytes.

Benadryl was found to be effective in one case,[37] but there was question as to whether its efficacy might not be attributed to its "antispasmodic action" than to its antihistaminic effects. Beneficial results also have been obtained by avoidance of cold, by desensitization to cold and by the use of vasodilators.[59]

Cold hemagglutination with paroxysmal cold hemoglobinuria may be confused with syphilitic hemoglobinuria. Its cutaneous manifestations, except for cold urticaria, also may mimic those of cryoglobulinemia Serologic tests for syphilis, the Donath-Landsteiner test for cold hemolysins, cold hemagglutination titers and cryoglobulin determinations help to differentiate these conditions A few reports have been published of the coexistence of cryoglobulinemia, high cold agglutinin titers and hemolytic anemia, but the significance of such association is not known

ESSENTIAL COLD URTICARIA

By far the most common form of cold urticaria is that which develops without demonstrable cold hemolysins, cold hemagglutinins or cryoglobulins in the serum.

In these cases cold sensitivity manifests itself exclusively either by wheal formation or diffuse swelling in areas exposed to cold. The wheals represent the typical "triple response," as described by Lewis, with primary local vasodilation, local wheal formation and red flare. It is known that liberation of hista-

mine, which is the last link in the chain of events, is responsible for this reaction.

Two groups of cold urticaria can be distinguished the acquired form and the congenital (familial) type

Acquired Cold Urticaria. *Clinical Features.* In most cases the onset is rather sudden without a prodrome This sudden onset remains unexplained in most cases However, a great variety of eliciting factors has been enumerated in the literature. Apparently they act as trigger mechanisms in the development of the disease In three cases[7,9,21] horse serum injections and serum sickness preceded the onset. In three sisters with typical uneventful measles, cold urticaria developed immediately following recovery and lasted for one year, when it terminated spontaneously[86] There are scattered reports of other alleged eliciting factors such as scarlatina,[17] chickenpox,[22] previous dermatitis,[82] childbirth,[38] the taking of prolonged hot showers,[72] the bite of an unidentified insect or jellyfish[64] and emotional factors.[1] In isolated cases cold urticaria was found to be *manifest only* under specific conditions, such as after eating custard,[illegible] pork blood sausage[94] or menthol lozenges[26] It has been found also in association with ascaris infestation,[32] foci of infection,[83] uterine fibroids,[70] hypoacidity [illegible] and hypothyroidism,[11] and cleared upon removal of these conditions However, in the majority of cases no precipitating or underlying factors could be determined

For the most part, cold urticaria is limited to the sites of contact with cold. The face and the exposed parts of the extremities are involved primarily However, with high degrees of sensitivity generalized urticaria may follow localized exposure to cold The lib-

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toms, such as swelling of the mouth and the lips, dysphagia and abdominal cramping, may follow inhalation of cold air or ingestion of cold liquids or solids.

The triple response appears only after exposure to cold has ceased, obviously because vasoconstriction does not permit development of a wheal As in other physical urticarias, pseudopods usually are lacking.

There may be a difference in the cutaneous hypersensitivity to cold air and to cold solids or liquids, some individuals are sensitive to one only of these or exhibit different degrees of sensitiveness to them. Apparently there is no critical environmental or skin temperature at which the eruption appears Humidity and wind velocity seem to have some influence, but whether or not this influence is exerted *via* changes in skin temperature has not been investigated. In general, an environmental temperature of 20° C is regarded as the upper limit for eliciting a whealing reaction However, in some cases the sensitivity seems to be so great that environmental temperatures as high as 26° C (or even higher [34]) can be urticariogenic. It has been claimed that the threshold stimulus cannot be expressed in terms of absolute environmental or skin temperatures but that the actual stimulus, as is the case with cold sensation, is the temperature gradient within a limited period of time [34] In other words, a sudden drop in temperature to a certain level in warm weather may produce symptoms, yet the same temperature level may not produce a reaction in cold weather In any case, extreme degrees of cold usually are not necessary to elicit the pathologic reaction in people afflicted with this disorder.

The length of exposure required to elicit a wheal

eration of excess histamine into the circulation is the most probable explanation of this generalization. Frequently it has been shown[10, 28, 50] that cold urticaria remains restricted to the site of cold exposure when the venous return from the exposed part is occluded by a tourniquet. Following release of the tourniquet, generalized urticaria and/or systemic effects occur. The most plausible explanation of this phenomenon is excess histamine liberation with subsequent hematogenous spread. However, there also is a possibility that, by reflex vasoconstriction, localized cooling can cause a critical drop in skin temperature over the entire body surface, with resultant generalized whealing.

If the exposure to cold is more or less generalized, *as is the case in swimming or in taking a shower with* cold water, the generalized urticaria frequently is accompanied by systemic signs of histamine shock. A fall in blood pressure, tachycardia, flushing of the face, increased gastric acidity and syncope with peripheral vascular collapse may occur. In reviewing the literature Horton *et al*[28] collected 15 such cases of syncope following swimming in cold water and added nine of their own. The danger of drowning under such conditions is great.

In some cases[52, 53] it has been observed that parts exposed frequently to cold display greater urticarial sensitivity to cold than do other parts This type of "conditioning" has not been reported in other physical allergies.

Mucous membranes may be involved in sensitivity to cold, either with or without cutaneous *hypersensitivity*. Respiratory symptoms, such as nasal stuffiness, cough and dyspnea, and gastro-intestinal tract symp-

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varies from a few seconds to several minutes and usually is in inverse proportion to the degree of cold Paradoxically exposure to excessively low temperatures or prolonged contact with cold may abolish the reaction.

Originally Duke stressed the importance of an atopic family or a personal history in individuals with physical allergy. A review of the literature by us has revealed an atopic family history in one-third of the cases of cold urticaria in which inquiry into atopic history was mentioned.

Diagnosis. The diagnosis of cold urticaria usually is simple when a well-established and correlated history is presented The diagnosis may be confirmed by application of cold water in a test tube or ice to that part of the skin which by history is sensitive to cold. Contact with water at from 6 to 10° C should last from six to ten minutes, with ice exposure, 20 to 30 seconds usually is sufficient

Laboratory findings usually are not remarkable Eosinophilia has been reported in a few cases[19, 20, 30, 41] but not consistently enough to make it useful diagnostically. Intracutaneous tests with material allergens are negative unless the subject has concomitant allergies In general, no reactions are elicited with physical stimuli other than cold

Treatment. The management of this condition often is difficult. Of course, the patient should be advised to avoid cold exposure as much as possible, but in most cases this is not practicable The dangers of cold showers, swimming and other generalized exposures to low temperatures must be emphasized

"Desensitization" to cold may be attempted The basis for this treatment is the development of refrac-

toriness of a site to repeated cold exposures. Kierland[34] recommends immersion of the patient's hand or foot in water at 17° C for from two to five minutes once or oftener daily and gradually reducing the temperature of the water to a minimum of 7° C. over a period of from three to four weeks If reactions occur during treatment, heat may be applied The "desensitization" or tolerance developed usually is only partial and temporary

"Desensitization" with repeated injections of histamine also has been used therapeutically with allegedly satisfactory results in some cases.[10, 24, 62] We find it difficult to accept the premise that the human body can be desensitized to one of its physiologic products. Peters and Horton[50] demonstrated that though a site might fail to produce a wheal with repeated cold exposures, injection of histamine into these areas still produced a wheal, showing that there was no refractoriness to histamine itself

Histaminase was used with some limited success in the years prior to the advent of antihistamines but now has been replaced by these newer drugs For the most part, antihistamines have been successful in controlling or at least ameliorating the condition[44, 47, 48, 60] Cases of moderate severity can be controlled by relatively small doses, such as 50 mg. of Benadryl or Pyribenzamine three or four times daily One of our cases is well controlled with Chlor trimeton 4 mg. three times a day Inadequate dosage may well account for the failures reported[1, 48, 61] Patients have been noted to develop a tolerance to the antihistamines, so that increasing doses or a change of the compound may be needed to control the symptoms[49]

It is good practice to use a combination of at least

two antihistamines simultaneously when large doses are required, on the assumption that harmful side effects are less likely to occur with small doses of two or three drugs, especially if their chemical structures differ substantially, than with a large dose of a single antihistamine.

Only a few reports of cases treated with ACTH or cortisone have been published[27, 32, 61] The results have been disappointing. Samsoe-Jensen[61] failed to observe any clinical response in a patient receiving 200 mg. of cortisone daily.

Congenital (Familial) Cold Urticaria. Kile and Rusk,[35] Urbach *et al.*,[69] Witherspoon *et al.*,[74] and *Rodin and Bluefarb*[55] *have published* reports of familial urticaria due to cold that was transmitted as a non-sex-linked mendelian dominant through four generations. In these cases the urticaria was present from birth or shortly thereafter and continued throughout life. Constitutional symptoms such as chills, fever, arthralgia and headache often accompanied the urticaria. Cold air seemed to be more effective than cold water in eliciting wheals Passive transfer tests and tests for cryoglobulins, cold agglutinins and cold hemolysins were *negative in those* patients tested.

Rostenberg[58] questions whether or not familial cold urticaria represents a true allergic state, since true allergies rarely are transmitted from generation to generation with such strikingly identical clinical pictures as in this type of cold urticaria

DISCUSSION

That histamine mediates the development of cold urticaria has been well accepted on the basis of Lewis's

original studies on H substance.[53] The work of Horton *et al* [28] showed that development of cold urticaria released into the blood stream a substance that produced the signs and the symptoms of histamine shock. The efficacy of antihistamines in relieving the symptoms of this type of cold sensitivity further substantiates this theory.

In cold urticaria, as in other "physical allergies," the question arises as to whether or not this is a true allergic condition based on an antigen-antibody reaction. Many workers have been reluctant to accept an allergic mechanism, principally because of failure or difficulty in producing positive passive transfer tests.

A review of the domestic and the foreign literature from 1929 to 1955 produced 54 reports of attempted *passive transfer in cold urticaria. Of these attempts 30 were positive and 24 were negative.* This finding of 56 per cent positivity compares quite favorably with the results obtained in passive transfer studies with sera of patients suffering from urticarial drug eruptions that presumably have an allergic basis.

In passive transfer studies the challenge with cold should be made within two to five hours after deposition of the patient's serum into the recipient's skin.[51] Longer intervals of time between transfer of serum and challenge may have accounted for some of the negative results reported, although a few positive results have been reported with challenges made from 24 to 36 hours after serum deposition.[54,55] Even with early challenge the reaction may be weak.

The positivity of the passive transfer tests can be increased by using serum obtained after cold exposure[11,4] and in Wolter's case[2] the transfer succeeded only with serum taken after cold exposure

Rajka and Asboth[54] recommend reagin-fixation methods such as injection of serum into sites cooled previously with ice and injection of serum together with vasoconstrictors such as Adrenalin to enhance the degree of reaction and the number of positive tests These authors found the passive transfer tests to be positive with sera diluted 1:20 Administration of Pyribenzamine abolished the response. Samsoe Jensen[61] also found positive passive transfer tests with a serum dilution of 1:20. Cortisone 200 mg. daily failed to lower the titer.

While the simplest interpretation of a positive passive transfer is that antibodies have been transferred with the patient's serum into the skin of the recipient, it should be conceded that other interpretations also are possible, particularly in the case of "physical allergies." Transfer of abnormal serum constituents *other than antibodies might yield the same results* This problem has been discussed ably in the introductory chapter of this monograph. We are inclined to accept the theory that "physical allergies" are true allergies in which the antibody is formed against a normal metabolite produced in everybody's skin under the influence of the particular physical agent. However, this theory has not been proved directly as yet except in the case of cholinergic heat urticaria Sherman and Seebohm[64] failed to obtain an urticarial reaction when they mixed an extract of frozen skin with the cold-sensitive patient's serum and injected the mixture into the skin of normal individuals at room temperature. Thus, no potential antigen could be demonstrated in cooled skin. Also, if it is true that a substance is formed in cooled skin to which cold urticaria patients are sensitive, injection of their

rum into previously cooled skin of normal people (reverse passive transfer test) should cause an urticarial reaction According to the work of Rajka and Asboth [54] and Sherman and Seebohm,[65] this is not the case.

In a somewhat modified hypothesis, cold urticaria could be regarded as being based on an antigen-antibody mechanism by postulating that low temperatures merely facilitate the reaction between an antibody and a pre-existing antigen present in normal human skin In some ways this mechanism would be similar to those acting in cold hemolysis and cold hemagglutination In these instances low temperatures promote the reactions between antibody and a pre-existing antigen in the erythrocytes rather than produce a new antigen Previous cooling of red cells does not cause them to react with cold agglutinins or cold hemolysins when added to them at room temperatures It seems that the reaction takes place only at cold temperatures In support of this concept, Sherman and Seebohm [65] demonstrated the ability of cells in excised normal skin to adsorb at cold temperatures the cold sensitizing factor from serum of their patient with cold urticaria, so that the serum was no longer capable of producing a positive passive transfer test. This is analogous to the adsorption of cold hemolysin by red blood cells in the cold, as described by Harris et al.

Although uncommon, cold urticaria is not a rare disease It merits more intensive research

SUMMARY

1 Urticarial hypersensitivity to cold occurs in cryoglobulinemia, in syphilitic paroxysmal cold hemo-

globinuria and in essential cold urticaria. The presence of cold agglutinins in the blood is not associated with such sensitivity.

2. Clinical features, diagnosis and management of essential cold urticaria are described.

3. In about one-half of the cases reported, positive passive transfer tests were obtained in cold urticarias. The problem of whether or not this finding indicates true allergy is discussed.

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